LIGANDS FOR I7L AS MODULATORS OF ORTHOPOX VIRUSES AND METHODS FOR DISCOVERY THEREOF

RELATED APPLICATIONS

This patent application claims priority to provisional patent application Serial No. 60/529,384, filed December 12, 2003. The disclosure of provisional patent application Serial No. 60/529,384 is hereby incorporated by reference in its entirety.

FIELD OF INVENTION

The present invention relates to methods of discovery. The methods may be advantageous for discovering compounds that alter a biological activity of a molecule of interest. The present invention also provides anti-viral compounds that may be identified using such methods.

BACKGROUND

Viruses are obligatory intracellular parasites that can take over host cell transcription and translation to produce new viral particles. Interception of viral-driven transcription or translation, including both pre- and post-translation events, may result in crippling of the virus.

Smallpox, a member of the orthopox family of viruses, has recently resurfaced as a public heath concern. Until the last several years, the production of vaccines and therapeutics to combat smallpox was not considered necessary, as the last known case of smallpox was reported in 1977 in Somalia. In fact, universal vaccination in the United States was discontinued in 1972, since the risk of complications from the vaccine was actually greater than the risk of being infected with the disease. As a result, a portion of the population has never been vaccinated and thus, may be susceptible to infection by newly emerging strains of smallpox and other orthopox viruses.

Small molecule chemotherapy may be an alternative to vaccination for the prevention and/or treatment of orthopox viruses. For example, since the discovery of non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs), several classes of organic molecules have been designed to combat viral infections by inhibiting targets responsible for viral replication and morphogenesis. Due to the highly homologous nature of the orthopox family, therapeutics developed against smallpox may also be potential candidate therapies for related viruses such as monkeypox, a virus that recently reemerged in Africa and spread to the United States

by importation of exotic animals, and mulluscipox virus, a common cutaneous infection that may be problematic in immunocompromised individuals.

To date, no small molecule antiviral drug has proven to be effective in the treatment of smallpox. The only antiviral agent currently approved for use against orthopoxviruses is cidofovir, a DNA polymerase inhibitor that may be used to treat cytomegalovirus and other herpes viruses. However, the usefulness of cidofovir may be limited in that the drug exhibits low bio-availability when administered orally, and thus, must be administered intravenously (Cundy, K.C., 1999, *Clin. Pharmacokinet.*, 36:127-143).

Because proteolysis catalyzed by viral-encoded proteases can be a necessary step in the development cycle of most viruses, protease inhibitors may provide another class of drugs that act as anti-viral agents. For example, protease inhibitors have proven to be effective against human immunodeficiency virus (HIV), influenza, hepatitis C, and rhinovirus enzymes.

During replication of vaccinia virus (VV), a prototypic member of the orthopox family, two types of proteolytic processing occur: formative and morphogenic. I7L is a protease involved in the maturation of the core protein of the orthopoxvirus virion. I7L appears to be involved in an obligatory morphogenic cleavage of three major structural proteins found in the mature VV virion: 4a, 4b, and 25K. I7L protease is a 47 kDa cysteine protease that contains putative catalytic histidine and cysteine residues embedded in a conserved region containing an aspartic acid residue. The gene for I7L appears to be highly conserved among poxviruses, as the identity among I7L genes between variola virus and vaccinia virus is 99%, and I7L genes from all orthopox viruses also appear to possess a large degree of homology. The importance of I7L has been underscored in studies with temperature-sensitive (ts) viruses in which the I7L gene has been shown to be essential for viral replication using a conditional lethal mutant, *ts*16, that maps to this locus (Byrd, C.M., et al., Virology, 2003, 77:11279-11283; Byrd, C.M., et al., Virology, 2002, 76:8973-8976).

The resurgence of smallpox virus, and the threat of the use of smallpox virus as a weapon of biological warfare, has resulted in smallpox and other orthopox viruses reemerging as important public health concerns. The identification of agents that can either treat the symptoms caused by orthopoxviruses, or halt the spread of these viruses is of paramount importance. Thus, what is needed are methods for the

development of agents that may be used to target orthopoxviruses, such as smallpox. Such methods should allow for the rapid evaluation of large numbers of compounds such that the most effective compounds can be rapidly identified. In addition, such methods may provide a library of putative anti-viral agents. Such anti-viral agents may reduce or remove the threat of the virus as a weapon, and may act as a strong deterrent to those attempting to develop pox viruses as biological weapons.

SUMMARY

The present invention relates to methods of discovery that may be embodied in a variety of ways. In an embodiment, the methods are useful for discovering compounds that alter a biological activity of a compound of interest. The present also relates to these types of compound.

In one embodiment, the invention may comprise a method for identifying a compound having the ability to modulate virus propagation in a host cell. The virus may comprise an orthopox virus, such as smallpox virus, vaccinia virus, monkeypox virus, mulluscipox virus, or cowpox virus. The method may comprise a first step of generating a three-dimensional model of a protein, or a portion thereof, required for orthopox viability. Next, a three-dimensional model of a potential modulator compound of interest may be generated. Finally, the method may comprise determining at least one atomic interaction between the potential modulator compound and the protein, or a portion thereof, as defined by the three-dimensional models for each.

In one embodiment, the invention may comprise a method for identifying a compound that has the ability to modulate orthopox virus propagation in a host cell by inhibiting a viral I7L protease. The method may comprise the step generating a three-dimensional model of I7L protein, or a portion thereof. The method may further comprise generating a three-dimensional model of a potential modulator compound of interest. Next, the method may comprise determining the nature of at least one of the atomic interactions between the potential modulator compound and the I7L protein, or a portion thereof, as defined by the three-dimensional models for the potential modulator compound and I7L, protein or a portion thereof.

The present invention also provides a method of generating a three-dimensional model of a protein, or a portion thereof. The method may comprise the steps of providing an amino acid sequence of the protein of interest, and comparing the amino acid sequence of the protein of interest to the amino acid sequence of other

proteins for which a three-dimensional structure has been defined to identify a second protein having a predetermined level of sequence identity to the protein of interest. Once a second protein having a known three-dimensional structure has been identified, the method may further include the step of aligning conserved residues from the protein of interest with conserved residues from the second protein. Next, the sequence for the protein of interest may be threaded along the three-dimensional structure of the second protein, such that the position of at least two conserved residues from both proteins are aligned.

The present invention also comprises a computer model for I7L protein or a portion thereof, comprising structural coordinates for a three-dimensional model for I7L protein, or a portion thereof, operable to be visualizable on a computer screen.

The present invention also provides anti-viral agents. In one embodiment, the anti-viral agents may inhibit poxvirus. The anti-viral agent may comprise a pharmacophore. For example, in one embodiment, the present invention may comprise a pharmacophore comprising at least one atom or molecular group that interacts with at least one atom or molecular group of I7L protein, or a portion thereof. Or the anti-viral agent may comprise a compound. For example, in one embodiment, the present invention may comprise a compound comprising at least one atom or molecular group that interacts with at least one atom or molecular group of I7L protein, or a portion thereof. In one embodiment, the compound interacts with I7L to modulate the activity of I7L. For example, the compound may be a compound identified by docking a computer representation of the compound, or a synthetic variant thereof, with a computer representation of a three-dimensional structure of I7L protein, or a portion thereof. In one embodiment, the three-dimensional structure of I7L, or a portion thereof, is defined, at least in part, by Table 2. In yet another embodiment, the present invention may comprise a pharmaceutical composition. For example, the present invention may comprise a pharmaceutical composition comprising a compound identified by docking a computer representation of the compound with a computer representation of a structure of I7L protein, or a portion thereof.

The present invention also comprises a method of conducting a drug-discovery business. The method may comprise the step of generating a three-dimensional structural model of a target molecule of interest on a computer. Also, the method may comprise generating a three-dimensional structural model of a potential modulator

compound of the target molecule on a computer, and docking the model for the potential modulator compound with the target molecule so as to minimize the free energy of the interaction between the target molecule and the potential modulator. In this way, a modulator compound that may interact with the target may be identified. The method may also include the subsequent steps of providing a modified structure for the modulator compound of interest, and assessing whether the modified structure has a lower free energy of interaction with the target than the original modulator compound.

In another embodiment, the present invention comprises treatment of orthopox viral infections using compounds identified by the methods and systems of the present invention. The orthopox viruses may include smallpox virus or other orthopox virses such as, but not limited to, vaccinia virus, monkeypox, or cowpox.

There may be advantages provided by certain embodiments of the present invention. For example, the methods of the present invention may provide a means to identify a plurality of putative pharmacological agents based upon the known three-dimensional structure of a target protein. Also, the present invention may provide a means to modify the structure of a putative pharmacological agent *in silico* to determine how such changes can effect the activity of the agent. Making such determinations *in silico* provides the ability to rapidly evaluate a large number of compounds. Also, making such determinations *in silico* allows for a rational approach to drug development, such that compounds may be systematically developed and their activity evaluated.

The present invention may provide compounds that may be used as pharmaceuticals for treating humans and animals suffering from, or potentially exposed to, infections caused by orthopox viruses, including smallpox, monkeypox and cowpox viruses. The compounds of the present invention may be used in combination therapy with other anti-viral agents. For example, anti-viral agents of the present invention that are protease inhibitors may be combined with other agents that act by other mechanisms. Also, the compounds of the invention may provide broad spectrum antiviral agents with a low level of toxicity and a high therapeutic index. Such compounds may further provide an antiviral agent that may be used against viral strains that are resistant to other types of antiviral agents such as agents that inhibit DNA replication or immunomodulators.

There are, of course, additional features of the invention, which will be described in more detail hereinafter. It is to be understood that the invention is not limited in its application to the specific details as set forth in the following description and figures. The invention is capable of other embodiments and of being practiced or carried out in various ways.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows a superposition of vaccinia virus (VV) I7L protease with the C-terminal domain of ULP1 protease in accordance with an embodiment of the present invention. I7L is shown as a solid ribbon and ULP1 is shown as a multi-lined ribbon. Hang point residues of ULP1 (His514, Cys580, Trp448) and I7L (His241, Cys328, Trp168) are shown. Darker shading indicates regions of the polypeptide or individual residues that are closer to the viewer, whereas lighter shading indicates regions of the polypeptide or individual residues that are farther away.

FIG. 2 shows a three-dimensional homology threading model of vaccinia virus (VV) I7L generated using the structure of the C-terminal portion of ULP1 protease in accordance with an example embodiment of the present invention. Darker shading indicates regions of the polypeptide or individual residues that are closer to the viewer, whereas lighter shading indicates regions of the polypeptide or individual residues that are farther away.

FIG. 3 shows a close-up view of the I7L ligand binding site in accordance with an example embodiment of the present invention. Darker shading indicates regions of the polypeptide or individual residues that are closer to the viewer, whereas lighter shading indicates regions of the polypeptide or individual residues that are farther away.

FIG. 4 shows a computed docking mode of a small organic molecule, TTP-A, on the surface of 17L protease in accordance with an embodiment of the present invention. TTP-A is shown in a meshed three-dimensional surface. Darker shading indicates regions of the polypeptide or individual residues that are closer to the viewer, whereas lighter shading indicates regions of the polypeptide or individual residues that are farther away.

FIG. 5 shows a view of the I7L ligand binding domain in accordance with an example embodiment of the present invention wherein Leu324 is represented in a space-filling representation. Darker shading indicates regions of the polypeptide or

individual residues that are closer to the viewer, whereas lighter shading indicates regions of the polypeptide or individual residues that are farther away.

FIG. 6 shows the structure of two small molecule organic compounds, TTP-A and TTP-B, that bind to I7L protein, or a portion thereof in silico and that have an anti-viral effect in a cell culture assay in accordance with an example embodiment of the present invention.

FIG. 7 shows a method for identification of potential therapeutic compounds targeted to I7L using *in silico* screening and optionally, biological screening, in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION

Definitions

The following definitions may be used to understand the description herein. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. Practitioners are particularly directed to Current Protocols in Molecular Biology (Ansubel) for definitions and terms of the art. Abbreviations for amino acid residues are the standard 3-letter and/or 1-letter codes used in the art to refer to one of the 20 common L-amino acids.

I7L is a protease involved in the maturation of the orthopox virus virion and thus, is required for orthopox virus viability and/or replication. Vaccinia virus I7L is a 423 amino acid cysteine protease that that catalyzes the cleavage of the 4a, 4b, and 25K structural proteins found in the mature vaccinia virus (VV) virion. The catalytic residues of wild-type I7L comprise a histidine and a cysteine embedded in a conserved region of the protein that contains an aspartic acid. I7L may be derived from a variety of sources, including orthopox viruses such as vaccinia virus, cowpox, camelpox, variola major, variola minor, monkeypox, ectromelia, sheeppox, lumpy skin, Yaba-like, swinepox, rabbit fibroma, myxoma, fowlpox, canarypox, armsacta moorei viruses. The enzyme may be from any source, whether natural, synthetic, semi-synthetic, or recombinant. A number of I7L proteins have been identified and cloned and these may be used in the methods of the invention. All of the I7L proteins characterized to date may be used in the methods of the present invention.

An I7L protein or part thereof in the present invention may be a wild type enzyme or part thereof, a mutant enzyme or part thereof, or variant or homologue of such an enzyme. As used herein, the term "wild type" refers to a polypeptide having

a primary amino acid sequence which is identical with the native enzyme. The term "mutant" refers to a polypeptide having a primary amino acid sequence which differs from the wild type sequence by one or more amino acid additions, substitutions or deletions. A mutant may or may not be functional. As used herein, the term "variant" refers to a naturally occurring polypeptide which differs from a wild-type sequence. As used herein, when referring to a protein, the terms "portion" or "part" indicate that the polypeptide comprises a fraction (or fractions) of the amino acid sequence referred to.

"Polypeptide" and "protein" are used interchangeably herein to describe protein molecules that may comprise either partial or full-length proteins.

As used herein, "small organic molecules" are molecules of molecular weight less than 2,000 Daltons that contain at least one carbon atom.

The term "vector" refers to a nucleic acid molecule that may be used to transport a second nucleic acid molecule into a cell. In one embodiment, the vector allows for replication of DNA sequences inserted into the vector. The vector may comprise a promoter to enhance expression of the nucleic acid molecule in at least some host cells. Vectors may replicate autonomously (extra chromosomal) or may be integrated into a host cell chromosome. In one embodiment, the vector may comprise an expression vector capable of producing a protein derived from at least part of a nucleic acid sequence inserted into the vector.

As used herein, the term "interact" refers to a condition of proximity between a ligand or compound, or portions or fragments thereof, and a portion of a second molecule of interest. The interaction may be non-covalent, for example, as a result of hydrogen-bonding, van der Waals interactions, or electrostatic or hydrophobic interactions, or it may be covalent.

As used herein, the term "atomic contacts" or "atomic interaction" refers to the inter-atomic contact between atoms in a test compound and atoms in a second molecule (e.g., the protein of interest) for which a three-dimensional model is made. The atomic interaction is governed by geometric and physiochemical complementarity as well as steric fit between the two molecules for which the atomic contacts/interaction is evaluated. Thus, an atomic interaction between a potential modulator compound and the I7L protein, or a portion thereof, comprises at least one atomic interaction selected from the group consisting of charge, electrostatic, hydrogen bond, and hydrophobic. The atomic interaction may be covalent bond. For

example, atomic interactions between I7L ligand binding domain and small molecules TTP-A and TTP-B are described, at least in part, by Tables 5 and 6, respectively.

As used herein, the term "docking" refers to a process by which a test compound is placed in close proximity with a second molecule (e.g., the protein of interest). Docking is also used to describe the process of finding low energy conformations of a test compound and a second molecule (e.g., the protein or polypeptide of interest, or portion thereof). Docking studies include molecular modeling studies aimed at finding a proper fit between a ligand and its binding site.

As used herein, the term "docking mode" refers to a favorable configuration of a test compound docked (e.g., positioned) within a given site on a molecule of interest.

As used herein, the term "hang point residues" refers to residues on a first molecule of known structure that are then used as anchors for the threading of a second molecule of unknown structure along the structure of the first molecule so as to determine a structure for the second molecule. For example, to determine a structure for I7L protein, or a portion thereof, residues Cys580, His514, and Trp448 of a ULP1 protein of known structure were the hang point residues that were aligned with Cys328, His241, and Trp168 of the I7L to determine the structure of I7L.

As used herein, the term "conserved residues" refers to amino acids that are the same among a plurality of proteins having the same structure and/or function. A region of conserved residues may be important for protein structure or function. Thus, contiguous conserved residues as identified in a three-dimensional protein may be important for protein structure or function. To find conserved residues, or conserved regions of 3-D structure, a comparison of sequences for the same or similar proteins from different species, or of individuals of the same species, may be made.

As used herein, the term "homologue" means a polypeptide having a degree of homology with the wild-type amino acid sequence. Homology comparisons can be conducted by eye, or more usually, with the aid of readily available sequence comparison programs. These commercially available computer programs can calculate percent homology between two or more sequences (e.g. Wilbur, W. J. and Lipman, D. J., 1983, *Proc. Natl. Acad. Sci. USA*, 80:726-730). For example, homologous sequences may be taken to include an amino acid sequences which in alternate embodiments are at least 75% identical, 85% identical, 90% identical, 95% identical, or 98% identical to each other.

The terms "identity" or "percent identical" refers to sequence identity between two amino acid sequences or between two nucleic acid sequences. Percent identity can be determined by aligning two sequences and refers to the number of identical residues (*i.e.*, amino acid or nucleotide) at positions shared by the compared sequences. Sequence alignment and comparison may be conducted using the algorithms standard in the art (*e.g.* Smith and Waterman, 1981, *Adv. Appl. Math.* 2:482; Needleman and Wunsch, 1970, *J. Mol. Biol.* 48:443; Pearson and Lipman, 1988, *Proc. Natl. Acad. Sci., USA*, 85:2444) or by computerized versions of these algorithms (Wisconsin Genetics Software Package Release 7.0, Genetics Computer Group, 575 Science Drive, Madison, WI) publicly available as BLAST and FASTA. Also, ENTREZ, available through the National Institutes of Health, Bethesda MD, may be used for sequence comparison. In one embodiment, the percent identity of two sequences may be determined using GCG with a gap weight of 1, such that each amino acid gap is weighted as if it were a single amino acid mismatch between the two sequences.

As used herein, a polypeptide or protein "domain" comprises a region along a polypeptide or protein that comprises an independent unit. Domains may be defined in terms of structure, sequence and/or biological activity. In one embodiment, a polypeptide domain may comprise a region of a protein that folds in a manner that is substantially independent from the rest of the protein. Domains may be identified using domain databases such as, but not limited to PFAM, PRODOM, PROSITE, BLOCKS, PRINTS, SBASE, ISREC PROFILES, SAMRT, and PROCLASS.

As used herein, "ligand binding domain" (LBD) refers to a domain of a protein responsible for binding a ligand. The term "ligand binding domain" includes homologues of a ligand binding domain or portions thereof. In this regard, deliberate amino acid substitutions may be made in the LBD on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the binding specificity of the ligand binding domain is retained. For example, for I7L protein, the ligand binding domain may comprise residues 110-423 of vaccinia virus I7L protein.

As used herein, the "ligand binding site" comprises residues in a protein that directly interact with a ligand, or residues involved in positioning the ligand in close proximity to those residues that directly interact with the ligand. The interaction of residues in the ligand binding site may be defined by the spatial proximity of the

residues to a ligand in the model or structure. The term "ligand binding site" includes homologues of a ligand binding site or portions thereof. In this regard, deliberate amino acid substitutions may be made in the ligand binding site on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the binding specificity of the ligand binding site is retained. For I7L, the ligand binding site may be defined as comprising those residues in Table 1. For example, the ligand binding site may be defined as comprising those residues in Table 1 and any other residues that are within a 3 angstrom radius of any one of the residues in Table 1.

As used herein, "catalytic domain" refers to a domain of a protein responsible for binding a substrate or that is involved in the catalytic mechanism. The term "catalytic domain" includes homologues of a catalytic binding domain or portions thereof. In this regard, deliberate amino acid substitutions may be made in the catalytic domain on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the binding specificity of the catalytic site within the catalytic domain.

As used herein, the "catalytic site" refers to a region of the catalytic domain that directly associates with a substrate or that is involved in the catalytic mechanism. For example, it may be a region of I7L that is responsible for binding a substrate. With reference to the models and structures of the present invention, residues in a catalytic site may be defined by their spatial proximity to a substrate in the model or structure. The term "catalytic site" includes homologues of a catalytic site, or portions thereof. In this regard, deliberate amino acid substitutions may be made in the catalytic domain on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the substrate specificity of the catalytic site is retained. For example, for I7L, the catalytic site may be included as part of the ligand binding site to include at least some those residues listed in Table 1.

As used herein, a "ligand" refers to a molecule or compound or entity that associates with a ligand binding domain, including substrates or analogues or parts thereof. As described herein, the term "ligand" may refer to compounds that bind to the protein of interest. A ligand may be a modulator. Or, a ligand may not have a biological effect. Or, a ligand may block the binding of other ligands thereby inhibiting a biological effect. Ligands may include, but are not limited to, small

molecule inhibitors of the activity of protein. These small molecules may include peptides, peptidomimetics, organic compounds and the like. For proteases, ligands may also include polypeptide and protein substrates.

As used herein, a "modulator compound" refers to a molecule which changes or alters the biological activity of a molecule of interest. A modulator compound may increase or decrease activity, or change the physical or chemical characteristics, or functional or immunological properties, of the molecule of interest. For I7L, a modulator compound may increase or decrease activity, or change the characteristics, or functional or immunological properties of the I7L, or a portion threof A modulator compound may include natural and/or chemically synthesized or artificial peptides, modified peptides (e.g., phosphopeptides), antibodies, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, glycolipids, heterocyclic compounds, nucleosides or nucleotides or parts thereof, and small organic or inorganic molecules. A modulator compound may be an endogenous physiological compound or it may be a natural or synthetic compound. Or, the modulator compound may be a small organic molecule. The term "modulator compound" also includes a chemically modified ligand or compound, and includes isomers and racemic forms.

The terms "structural coordinates" or "atomic coordinates" as used herein refers to a set of values that define the position of one or more amino acid residues or molecules with reference to a system of axes. A data set of structural coordinates defines the three dimensional structure of a molecule or molecules. Structural coordinates can be slightly modified and still render nearly identical three dimensional structures. A measure of a unique set of structural coordinates is the root-mean-square deviation of the resulting structure. In alternate embodiments, structural coordinates that render three dimensional structures that deviate from one another by a root-mean-square deviation of less than 3 angstroms, or less than 2.0 angstroms, or less than 0.5 angstroms, or less than 0.3 angstroms, may be viewed by a person of ordinary skill in the art as identical. Variations in structural coordinates may be generated because of mathematical manipulations of the structural coordinates of I7L as described herein. For example, the structural coordinates of Tables 2-4 may be manipulated by crystallographic permutations of the structural coordinates, fractionalization of the structural coordinates, integer additions or subtractions to sets of the structural coordinates, inversion of the structural coordinates or any

combination of the above. Variations in structure due to mutations, additions, substitutions, and/or deletions of the amino acids, or other changes in any of the components that make up a structure of the invention may also account for modifications in structural coordinates. If such modifications are within the standard error as compared to the original structural coordinates, the resulting structure may be considered to be the same or equivalent. Therefore, a ligand that bound to a ligand binding domain of an I7L would also be expected to bind to another ligand binding domain whose structural coordinates defined a shape that fell within the margin of error defined by the first structure. Such modified structures of a ligand binding domain are also within the scope of the invention. For example, using the surface topology of a group of ligands, such as low-energy binding modes of TTP-A and TTP-B, which exhibit effector quality (agonist or antagonist) can be overlapped and the contours of all TTP-A and TTP-B averaged into a union surface. This union surface of a ligand is expected to be complementary to the surface mold of the corresponding binding site of I7L enzyme.

As used herein, a structural "model" of a protein of interest, a polypeptide of interest, or any other compound of interest, may be in two or three dimensions. For example, a computer model may be in three dimensions despite the constraints imposed by a computer screen, if it is possible to scroll along at least a pair of axes, causing rotation of the image. Also, a model of a protein or chemical compound of interest may be defined by the structural coordinates for the protein or compound of interest.

As used herein, the terms "modeling" or "generating a model" includes the quantitative and qualitative analysis of molecular structure and/or function based on atomic structural information and interaction models. The term may include conventional numeric-based molecular dynamic and energy minimization models, interactive computer graphic models, modified molecular mechanics models, distance geometry, and other structure-based constraint models.

The term "substrate" refers to the molecule or compound that is the target of an enzyme. For I7L, a substrate may include proteins and polypeptides cleaved by the I7L protease and includes the 4a, 4b, and 25K structural proteins of vaccinia virus.

The term "peptide mimetics" are structures which serve as substitutes for peptides in interactions between molecules (Morgan et al., 1989, *Ann. Reports Med. Chem.*, 24:243-252). Peptide mimetics may include synthetic structures that may or

may not contain amino acids and/or peptide bonds but that retain the structural and functional features of a peptide, or agonist, or antagonist. Peptide mimetics also include peptoids, oligopeptoids (Simon et al., 1972, *Proc. Natl. Acad, Sci., USA*, 89:9367); and peptide libraries containing peptides of a designed length representing all possible sequences of amino acids corresponding to a peptide, or agonist or antagonist of the invention.

The term "treating" refers to improving a symptom of a disease or disorder and may comprise curing the disorder, substantially preventing the onset of the disorder, or improving the subject's condition. The term "treatment" as used herein, refers to the full spectrum of treatments for a given disorder from which the patient is suffering, including alleviation of one, most of all symptoms resulting from that disorder, to an outright cure for the particular disorder or prevention of the onset of the disorder.

As used herein, "TC50" is the concentration at which 50% of the cells display signs of cytotoxicity. Also, "IC50" is the concentration at which there is 50% inhibition of the measured effect of interest. For I7L, "IC50" is the concentration at which there is 50% inhibition of viral cytopathic effect. The therapeutic index, "TI," is a ratio of the TC50 to the IC50. Thus, clinical beneficial drugs are generally those that have a high TI.

As used herein, "pharmacophore" is a collection of steric and elctronic features that are necessary to ensure the optimal supramolecular interactions with a specific biological target structure. A pharmacophore may comprise a structural definition that comprises a set of active molecules. For example, using the surface topology of a group of ligands, such as low-energy binding modes of TTP-A and TTP-B, which exhibit effector quality (agonist or antagonist) can be overlapped and the contours of all TTP-A and TTP-B averaged into a union surface that comprises a pharmacophore. This pharmacophore is expected to be complementary to the surface mold of the corresponding binding site of I7L enzyme.

As used herein, an "effective amount" as used herein means the amount of an agent that is effective for producing a desired effect in a subject. The term "therapeutically effective amount" denotes that amount of a drug or pharmaceutical agent that will elicit the therapeutic response of an animal or human that is being sought. The actual dose which comprises the effective amount may depend upon the

route of administration, the size and health of the subject, the disorder being treated, and the like.

The term "pharmaceutical composition" is used herein to denote a composition that may be administered to a mammalian host, *e.g.*, orally, topically, parenterally, by inhalation spray, or rectally, in unit dosage formulations containing conventional non-toxic carriers, diluents, adjuvants, vehicles and the like. The term "parenteral" as used herein, includes subcutaneous injections, intravenous, intramuscular, intracisternal injection, or by infusion techniques.

The term "a" or "an" as used herein may refer to more than one object unless the context clearly indicates otherwise. The term "or" is used interchangeably with the term "and/or" unless the context clearly indicates otherwise.

Ligands for I7L as modulators of orthopox viruses

Embodiments of the present invention provide ligands for I7L as modulators of viruses and methods for discovery of such ligands. In one embodiment, the invention may comprise a method for identifying a compound having the ability to modulate orthopox virus propagation in a host cell. The method may comprise the steps of: (a) generating a three-dimensional model of a protein required for orthopox viability, or a portion thereof; (b) generating a three-dimensional model of a potential modulator compound of interest; and (c) determining at least one atomic interaction between the potential modulator compound and the protein, or a portion thereof, as defined by the three-dimensional models of each.

The virus may comprise an orthopox virus, such as smallpox virrus, vaccinia virus, monkeypox virus, mulluscipox virus, cowpox virus, camelpox virus, variola major virus, variola minor virus, ectromelia virus, sheeppox virus, lumpy skin virus, Yaba-like virus, swinepox virus, rabbit fibroma virus, myxoma virus, fowlpox virus, canarypox virus, or amsacta moorei virus. In one example embodiment, the virus is smallpox virus. The protein may be any protein that is required for viability of the virus in a host cell. For example, the protein may be a protease that is required for formation or morphogenesis of the virus. Or, the protein may be required for DNA replication. The protein may be a cysteine protease. In one example embodiment, the protein is an I7L protease, such as vaccinia virus I7L protein.

The method may be performed using a computer. Thus, in one embodiment, the method comprises the steps of: (a) generating a three-dimensional computer model of the protein, or a portion thereof; (b) generating a three-dimensional

computer model of the potential modulator compound of interest; (c1) using a computer to dock the three-dimensional model of the potential modulator compound within the model of the protein or a portion thereof; and (c2) quantifying at least one atomic interaction between the potential modulator compound and the protein, or a portion thereof.

The method further allows for varying the structure of the potential modulator compound to determine how changes to the structure of the modulator may affect the fit of the compound with the protein of interest. Thus, the method may further comprise the steps of modifying the computer model of the potential modulator compound, and evaluating how modifying the computer model of the potential modulator compound changes at least one atomic interaction between of the model of the potential modulator compound and the model of the protein, or portion thereof. The potential modulator compound may be modified *in silico*. Thus, in one embodiment, the step of modifying the computer model of the potential modulator compound of interest comprises the step of searching a library of molecular structures for molecular fragments that can be linked to the potential modulator compound, wherein a molecular fragment comprises at least one atom. The method may further comprise linking a molecular fragment to the potential modulator compound to generate a modified compound. The modified compound may then be evaluated by docking the modified compound to the protein of interest and quantifying at least one atomic interaction between the modified compound and the protein of interest.

Also, the compound may be evaluated in a biological assay. Thus, the compound may be evaluated by its ability to inhibit virus growth or propagation. Also, the compound may be evaluated for cytotoxicity to uninfected cells. In one embodiment, the therapeutic index (TI), comprising the TC50 (concentration of the compound for which 50% of uninfected cells display signs of toxicity) divided by the IC50 (concentration at which the viral cytopathic effect is inhibited 50%) for the compound may be determined.

It may not be required to determine the entire structure of the protein of interest to identify compounds that may act as modulators of the protein. For example, the three-dimensional model of the protein of interest may comprise only a portion of the protein. Thus, the model may comprise the catalytic domain. Additionally or alternatively, the model may comprise a ligand binding domain. Additionally or alternatively, the model may comprise a ligand binding site.

Additionally or alternatively, the model may comprise the catalytic site. In some cases, the ligand binding site may also comprise the catalytic site.

It is also not necessarily required to determine how each amino acid of the entire structure of the protein of interest interacts with a potential modulator compound to identify compounds that may act as modulators of the protein. For example, the amino acid used to determine an atomic interaction between a potential modulator compound and the protein of interest may comprise a residue that is conserved in the protein of interest. Additionally, or alternatively, the amino acid used to determine an atomic interaction between a potential modulator compound and the protein of interest may comprise a residue that is present in, or affects the structure of, the catalytic domain and/or the catalytic site. Additionally, and/or alternatively, an amino acid used to determine an atomic interaction between a potential modulator compound and the protein of interest may comprise a residue that is present in, or affects the structure of, the ligand binding domain and/or the ligand binding site.

It has been shown that I7Lprotein (i.e., virion core protein proteinase) may be required for morphogenesis of orthopox viruses, and that without a functional I7L protein, propagation of the virus may be reduced. Thus, in one embodiment, the invention may comprise a method for identifying a compound having the ability to modulate orthopox virus propagation in a host cell, where the compound acts by inhibiting an I7L protease. The orthopox virus may comprise smallpox virrus, vaccinia virus, monkeypox virus, mulluscipox virus, cowpox virus, camelpox virus, variola major virus, variola minor virus, ectromelia virus, sheeppox virus, lumpy skin virus, Yaba-like virus, swinepox virus, rabbit fibroma virus, myxoma virus, fowlpox virus, canarypox virus, or amsacta moorei virus. In one example embodiment, the virus is smallpox virus. The method may comprise the steps of: (a) generating a three-dimensional model of a I7L protein, or a portion thereof; (b) generating a three-dimensional model of a potential modulator compound of interest; and (c) determining at least one atomic interaction between the potential modulator compound and the I7L protein, or a portion thereof, as defined by the three-dimensional models of the I7L protein, or a portion thereof, and the potential modulator compound of interest.

The model of I7L may comprise a variety of formats. In one embodiment, the model may comprise a three-dimensional structural model. Or, the model of I7L may comprise structural coordinates presented as the position of individual atoms of the

I7L protein, or a portion thereof, in space. For example, the model of I7L, or a portion thereof, may comprise the x, y, and z atomic coordinates as defined in Table 2.

The model of I7L protein, or a portion thereof, may be derived at least in part from the structure of a protein that comprises a similar function to I7L. The method of generating the computer model may comprise aligning the structure of the I7L protein, or a portion thereof, with a second cysteine protease. In one example embodiment, the second cysteine protease is ubiquitin-like protein 1 (ULP1) protease.

The model of I7L may be derived at least in part by aligning conserved sequences from the I7L protein, or a portion thereof, and a second protein. In one embodiment, the amino acids used to align the structure of the VV I7L protein or a portion thereof with ULP1 comprise His241, Asp248, and Cys328 of the I7L protein and His 514, Cys 580 and Trp448 of ULP1.

The method may be performed using a computer. Thus, in one embodiment, the method comprises the steps of: (a) generating a three-dimensional computer model of the I7L protein, or a portion thereof; (b) generating a three-dimensional computer model of the potential modulator compound; (c1) using a computer to dock the three-dimensional model of the potential modulator compound with the model of the I7L protein, or a portion thereof; and (c2) quantifying at least one atomic interaction between the potential modulator compound and the I7L as defined by the docking of the model of the potential modulator compound in the computer model of the I7L protein, or a portion thereof.

The method further allows for varying the structure of the potential modulator compound to determine how changes in the structure can affect the fit of the potential modulator compound with the protein of interest. Thus, the method may further comprise the steps of modifying the computer model of the potential modulator compound, and evaluating how modifying the computer model of the potential modulator compound affects the atomic interactions between of the model of the potential modulator compound and the model of the I7L protein, or portion thereof. The potential modulator compound may be modified *in silico*. Thus, in one embodiment, the step of modifying the computer model of the potential modulator compound of interest comprises the step of searching a library of molecular structures for molecular fragments that can be linked to the potential modulator compound, wherein a molecular fragment comprises at least one atom. The method may further

comprise linking a molecular fragment to the potential modulator compound to generate a modified compound. The modified compound may then be evaluated by docking the modified compound to the I7L protein, or a portion thereof, and determining the atomic interactions between the modified compound and the I7L protein.

It is not necessarily required to determine the entire structure of the protein of interest to identify compounds that may act as modulators of the protein. For example, the three-dimensional model of the protein of interest may comprise only a portion of the protein. Thus, the model may comprise the catalytic domain, or a portion thereof. For example, the model may comprise the catalytic site. Additionally or alternatively, the model may comprise a ligand binding domain, or a portion thereof, such as the ligand binding site. For I7L, the ligand binding site may also comprise the catalytic site.

It may not be required to determine how each amino acid of the entire structure of the I7L protein interacts with a potential modulator compound to identify compounds that may act as modulators of the I7L protein. For example, an amino acid used to determine the atomic interactions between a potential modulator compound and the I7L protein may comprise a residue that is conserved in the I7L protein. Additionally or alternatively, the amino acid used to determine an atomic interaction between a potential modulator compound and the I7L protein may comprise a residue that is present in, or affects the structure of, the catalytic domain and/or catalytic site. Additionally, or alternatively, an amino acid used to determine an atomic interaction between a potential modulator compound and the I7L protein may comprise a residue that is present in, or affects the structure of, the ligand binding domain and/or ligand binding site.

The residues that are used to determine the atomic interactions between a potential modulator compound and the I7L protein may comprise an amino acid that is active in catalysis. In one example embodiment, the amino acids used to determine an atomic interaction between a potential modulator compound and the I7L protease, or a portion thereof, comprises the catalytic cysteine of the I7L protein. In one embodiment, the atomic interactions with the catalytic cysteine may comprise a charge or electrostatic interaction. Additionally, or alternatively, the amino acids used to determine an atomic interaction between a potential modulator compound and the I7L protein, or a portion thereof, may comprise at least one of Cys328, His241,

Asp248, or Asp258 of the I7L protein. Additionally, or alternatively, the amino acids used to determine an atomic interaction between a potential modulator compound and the I7L protein, or a portion thereof, may comprise at least one of Leu324, Trp242, or Gln322 of the I7L protein. Or, the amino acids used to determine an atomic interaction between a potential modulator compound and the I7L protein, or a portion thereof, may comprise at least one of Gly329, Leu323, Ser240, Trp168, Asp194, Asn171, Ser173, Gln322, Met195, Ser326, Glu327, Leu239, Leu177, Asn199, Met169, Phe236, Ile203, or Met233 of the I7L protein. In one embodiment, the I7L protein, or portion thereof, is VV I7L.

Depending on the source of the protein used to generate a three-dimensional structure, there may be some variability in the absolute positioning of each amino acid. Still, it is to be expected that the relative positions of conserved amino acids may be maintained. For example, it has been found that there is a high degree in the catalytic triad sequence region (i.e., His241, Asp248, and Cys328 for VV I7L) of I7L proteins isolated from various poxviruses (Byrd, C.M. et al., 2004, J. Virol., 78:12147-12156) Thus, alignment of sequences immediately surrounding amino acids in the catalytic triad may comprise 95-99 percent sequence identity and identical spacing between the residues. Thus, for I7L, the amino acids used to determine the atomic interactions between a potential modulator compound and the I7L protein may comprise Cys(N), wherein position N corresponds to the catalytic cysteine. In one embodiment, the catalytic cyeteine corresponds to Cys328 of vaccinia virus I7L. Additionally, the amino acids used to determine the atomic interactions between a potential modulator compound and the I7L protein, or a portion thereof, may comprise at least one of His(N-87), Asp(N-80), or Asp(N-70) of the I7L protein, wherein position N corresponds to the catalytic cysteine of the I7L. Additionally, the amino acids used to determine the atomic interactions between a potential modulator compound and the I7L protein, or a portion thereof, may comprise at least one of Leu(N-4), Trp(N-86), or Gln(N-6) of the I7L protein, wherein position N corresponds to the catalytic cysteine of the I7L. Additionally, or alternatively, the amino acids used to determine the atomic interactions between a potential modulator compound and the I7L protein, or a portion thereof, may comprise at least one of Gly(N+1), Leu(N-5), Ser(N-88), Trp(N-160), Asp(N-134), Asn(N-157), Ser(N-155), Met(N-133), Ser(N-2), Glu(N-1), Leu(N-89), Leu(N-151), Asn(N-129), Met(N-159), Phe(N-

92), Ile(N-125) or Met(N-95), wherein position N corresponds to the catalytic cysteine of I7L.

The analysis may further employ a modified protein. Thus, the potential modulator compound may be evaluated for its interaction with a modified I7L protein, or portion thereof, wherein the I7L comprises at least one of an amino acid substitution, an amino acid deletion, or an amino acid insertion. In one embodiment, the amino acids used to determine the nature of the association between a test compound and the I7L protein, or a portion thereof, comprise at least one of wild-type or altered amino acid in the I7L protein corresponding to positions 168, 169, 171, 173, 177, 194, 195, 199, 203, 233, 236, 239, 240, 241, 242, 248, 258, 322, 323, 324, 326, 327, 328, or 329 of the wild-type VV I7L protein.

The nature of the interaction between the potential modulator compound and the protein of interest may be defined in terms of the atomic interaction between the compound and the protein of interest. In an embodiment, the atomic interaction between a potential modulator compound and the I7L protein, or a portion thereof, comprises at least one atomic interaction selected from the group consisting of charge, electrostatic, hydrogen bond, and hydrophobic. Alternatively, the atomic interaction between a potential modulator compound and the I7L protein, or portion thereof, may comprise at least two hydrogen bond atomic interactions, at least two hydrophobic atomic interactions, and at least one of a charge or electrostatic interaction. Or, the atomic interaction between a potential modulator compound and the I7L protein, or a portion thereof, may comprise at least three hydrogen bond atomic interactions, at least three hydrophobic atomic interactions, and at least one of a charge or electrostatic interaction. For example, for I7L, the atomic interactions between the modulator compound and I7L may comprise at least one of the atomic interactions described in Table 5. Or, the atomic interactions between the modulator compound and I7L may comprise at least one of the atomic interactions described in Table 6.

Also, the compound may be evaluated in a biological assay. Thus, the compound may be evaluated for inhibition of the virus. Also, the compound may be evaluated for cytotoxicity on uninfected cells. In one embodiment, the therapeutic index (TI), comprising the TC50 for the compound divided by the IC50 for the compound, may be determined.

The present invention also comprises a method of generating a three-dimensional model of a protein of interest, or a portion thereof. In one embodiment,

method may comprise the steps of: (a) providing an amino acid sequence of a protein of interest; (b) comparing the amino acid sequence of the protein of interest to the amino acid sequences of a plurality of other proteins; (c) identifying a second protein for which a three-dimensional structure has been defined, and that has a predetermined level of sequence identity to the protein of interest; (d) aligning conserved residues from the protein of interest with conserved residues from the second protein; and (e) threading the protein of interest along the three-dimensional structure of the second protein such that the position of at least two conserved residues from both proteins are aligned.

The protein aligned with the protein of interest may also comprise a protein having a similar sequence to the protein of interest. The level of sequence identity may range from at least 5% sequence identity, to more than 10% sequence identity, to more than 20% sequence identity. Also, the protein aligned with the protein of interest may comprise a protein having a similar function as the protein of interest.

In one example embodiment, the protein of interest may comprise I7L and the second protein comprises ubiquitin-like protein 1 (ULP1). Where the protein of interest is I7L, and the second protein is ULP1, the amino acids used to align the structure of the I7L protein with ULP1 may comprise His241, Asp248, and Cys328 of the I7L protease, and His 514, Cys 580 and Trp448 of ULP1.

The present invention may also comprise a structural model for a protein, or a portion of a protein, that may be manipulated using a computer. In one example embodiment, the present invention may comprise a computer model for I7L protein, or a portion thereof. The model may comprise atomic coordinates for a three-dimensional model for I7L, or a portion thereof, operable to be visualizable on a computer screen.

In one embodiment, the computer model of the protein of interest may comprise atomic coordinates presented as the position of individual atoms of the I7L protein, or a portion thereof, in space. For example, the model of I7L, or a portion thereof, may comprise at least some of the x, y, and z coordinates as defined in Table 2.

Also, the model may comprise a three-dimensional computer model of a potential modulator compound docked into the I7L structure such that the atomic interaction between the I7L and the potential modulator compound may be quantified. The atomic interactions between the I7L and the potential modulator compound may

be defined at least in part determining atomic coordinates for the potential modulator compound as it interacts with the I7L protein. In one embodiment, the three dimensional structure of a potential modulator compound may comprise at least some of the atomic coordinates as defined in Table 3 or Table 4.

The residues that are used to determine the atomic interactions between a potential modulator compound and the I7L protease may comprise an amino acid that is active in catalysis. In one example embodiment, the amino acid used to determine an atomic interaction between a potential modulator compound and the I7L protease, or a portion thereof, comprises the catalytic cysteine of the I7L protein. In one embodiment, the atomic interactions with the catalytic cysteine may comprise a charge or electrostatic interaction. Or, an amino acid used to determine an atomic interaction between a potential modulator compound and the I7L protease, or a portion thereof, may comprise at least one of Cys328, His241, Asp248, Asp258 of the I7L protein. Or, an amino acid used to determine an atomic interaction between a potential modulator compound and the I7L protease, or a portion thereof, may comprise at least one of Leu324, Trp242, or Gln322 of the I7L protein. Additionally, or alternatively, the amino acids used to determine an atomic interaction between a potential modulator compound and the I7L protease, or a portion thereof, may comprise at least one of Gly329, Leu323, Ser240, Trp168, Asp194, Asn171, Ser173, Gln 322, Met195, Ser326, Glu327, Leu239, Leu177, Asn199, Met169, Phe236, Ile203, or Met233 of the I7L protein. In one embodiment, the I7L protein, or portion thereof, is VV I7L.

Depending on the source of the protein used to generate a three-dimensional structure, there may be some variability in the absolute positioning of each amino acid. Still, it is to be expected that the relative positions of conserved amino acids may be maintained as there is a high degree in the catalytic triad sequence region (i.e., His241, Asp248, and Cys328 for VV I7L) of I7L proteins isolated from various poxviruses (Byrd, C.M. et al., 2004, J. Virol., 78:12147-12156) Thus, alignment of sequences immediately surrounding amino acids in the catalytic triad may comprise 95-99 percent sequence identity and identical spacing between the residues. Thus, for I7L, the amino acids used to determine the atomic interactions between a potential modulator compound and I7L protease may comprise Cys(N), wherein position N corresponds to the catalytic cysteine of I7L. Additionally, the amino acids used to determine the atomic interactions between a potential modulator compound and the

I7L protein, or a portion thereof, may comprise at least one of His(N-87), Asp(N-80), Asp(N-70), of the I7L protein, wherein position N corresponds to the catalytic cysteine of I7L. Or, the amino acids used to determine the atomic interactions between a potential modulator compound and the I7L protein, or a portion thereof, may comprise at least one of Leu(N-4), Trp(N-86), or Gln(N-6) of the I7L protein, wherein position N corresponds to the catalytic cysteine of I7L. Additionally, the amino acids used to determine the atomic interactions between a potential modulator compound and the I7L protease, or a portion thereof, may comprise at least one of Gly(N+1), Leu(N-5), Ser(N-88), Trp(N-160), Asp(N-134), Asn(N-157), Ser(N-155), Met(N-133), Ser(N-2), Glu(N-1), Leu(N-89), Leu(N-151), Asn(N-129), Met(N-159), Phe(N-92), Ile(N-125) or Met(N-95), wherein position N corresponds to the catalytic cysteine of I7L.

The computer model may further employ a modified protein. Thus, the potential modulator compound may be evaluated for its interaction with a modified I7L protein, or portion thereof, wherein the I7L comprises at least one of an amino acid substitution, an amino acid deletion, or an amino acid insertion. In one embodiment, the amino acids used to determine the nature of the association between a potential modulator compound and the I7L protein, or a portion thereof, comprise at least one of wild-type or altered amino acid in the I7L protein corresponding to positions 168, 169, 171, 173, 177, 194, 195, 199, 203, 233, 236, 239, 240, 241, 242, 248, 258, 322, 323, 324, 326, 327, 328, or 329 of the wild-type VV I7L protein.

The model may allow for the nature of the interaction between the potential modulator compound and the protein of interest to be defined in terms of the atomic interaction between the compound and the protein of interest. In an embodiment, the atomic interaction between a potential modulator compound and the I7L protein, or a portion thereof, comprises at least one atomic interaction selected from the group consisting of charge, electrostatic, hydrogen bond, and hydrophobic. Alternatively, the atomic interaction between a potential modulator compound and the I7L protein, or portion thereof, may comprise at least two hydrogen bond atomic interactions, at least two hydrophobic atomic interactions, and at least one of a charge or electrostatic interaction. Or, the atomic interaction between a potential modulator compound and the I7L protein, or a portion thereof, may comprise at least three hydrogen bond atomic interactions, at least three hydrophobic atomic interactions, and at least one of a charge or electrostatic interaction. For example, for I7L, the atomic interactions

between the modulator compound and I7L may comprise at least one of the atomic interactions described in Table 5. Or, the atomic interactions between the modulator compound and I7L may comprise at least one of the atomic interactions described in Table 6.

The model allows for varying the structure of the potential modulator compound to determine how changes in the structure of the modified compound can effect the fit of the compound with the protein of interest. Thus, the model may further comprise a three-dimensional model of a modified compound docked with the I7L structure. The potential modulator compound may be modified *in silico*. Thus, in one embodiment, the step of modifying the computer model of the potential modulator compound of interest comprises the step of searching a library of molecular structures for molecular fragments that can be linked to the potential modulator compound, wherein a molecular fragment comprise at least one atom, and linking the fragments to the compound. The modified compound may then be evaluated by docking the modified compound to the I7L protein, or a portion thereof, and determining the atomic interactions between the modified compound and the I7L protein.

The present invention also comprises a pharmacophore having a structure required to modify the protein of interest. For example, the pharmacophore may comprise at least one atom or molecular group that interacts with at least one atom or molecular group of I7L protein, or a portion thereof. Additionally, the three dimensional structure of the pharmacophore may comprise a plurality of atoms or molecular groups that interact with at least one atom or molecular group of a three-dimensional structure of I7L protein, or a portion thereof. To be active as a modulator of I7L, the pharmacophore may interact with the ligand binding domain of I7L, or a portion thereof, such as the ligand binding site. Additionally or alternatively, the pharmacophore may interact with the catalytic domain, or a portion therof such as the catalytic site of I7L.

The structure of the pharmacophore may vary with changes in the structure of the protein of interest. In one embodiment for I7L, the three-dimensional structure of I7L may be defined by at least some of the atomic coordinates as defined in Table 2. Where I7L is defined by the coordinates of Table 2, the spatial arrangement of atoms within the pharmacophore may comprise the atomic coordinates for at least one of the docking modes as defined in Table 3. In another example embodiment, the spatial

arrangement of atoms within the pharmacophore may comprise the atomic coordinates for at least one of the docking modes as defined in Table 4.

The nature of the interaction between the pharmacophore and the protein of interest may be defined in terms of the atomic interaction between the pharmacophore and the protein of interest. In an embodiment, the atomic interaction between a potential modulator compound and the I7L protein, or a portion thereof, comprises at least one atomic interaction selected from the group consisting of charge, electrostatic, hydrogen bond, and hydrophobic. Alternatively, the atomic interaction between a potential modulator compound and the I7L protein, or portion thereof, may comprise at least two hydrogen bond atomic interactions, at least two hydrophobic atomic interactions, and at least one of a charge or electrostatic interaction. Or, the atomic interaction between a potential modulator compound and the I7L protein, or a portion thereof, may comprise at least three hydrogen bond atomic interactions, at least three hydrophobic atomic interactions, and at least one of a charge or electrostatic interaction. For example, for I7L, the atomic interactions between the pharmacophore and I7L may comprise at least one of the atomic interactions described in Table 5. Or, the atomic interactions between the pharmacophore and I7L may comprise at least one of the atomic interactions described in Table 6.

The pharmacophore may be defined by its ability to interact with amino acids in the protein of interest that are important for catalytic activity and/or substrate binding. In one embodiment for an I7L pharmacophore, the interacting atom or molecular group for I7L may comprise the catalytic cysteine of I7L. In one embodiment, the atomic interactions with the catalytic cysteine may comprise a charge or electrostatic interaction. Or, the interacting atom or molecular group for I7L may comprise at least one of amino acids Cys328, His241, Asp248, Asp258, of I7L. Or, the interacting atom or molecular group for I7L may comprise at least one of amino acids Leu324, Trp242, and Gln322 of I7L. Additionally, or alternatively, the interacting atom or molecular group of I7L may comprise at least one of Gly329, Leu323, Ser240, Trp168, Asp194, Asn171, Ser173, Gln 322, Met195, Ser326, Glu327, Leu239, Leu177, Asn199, Met169, Phe236, Ile203, or Met233 of the I7L protein. In an embodiment, the I7L, or a portion thereof, comprises VV I7L.

Depending on the source of the protein used to generate a three-dimensional structure, there may be some variability in the absolute positioning of each amino acid. Still, it is to be expected that the relative positions of conserved amino acids

may be maintained. As described above, there is a high degree in the catalytic triad sequence region (i.e., His241, Asp248, and Cys328 for VV I7L) of I7L proteins isolated from various poxviruses (Byrd, C.M. et al., 2004, J. Virol., 78:12147-12156) Thus, alignment of sequences immediately surrounding amino acids in the catalytic triad may comprise 95-99 percent sequence identity and identical spacing between the residues. For I7L, the interacting group(s) used to determine the atomic interactions between the pharmacophore and I7L protein may comprise Cys(N), wherein position N corresponds to the catalytic cysteine of I7L. Additionally, the interacting group(s) may comprise at least one of His(N-87), Asp(N-80), Asp(N-70), of the I7L protein, wherein position N corresponds to the catalytic cysteine of I7L. Additionally, the interacting group(s) may comprise at least one of Leu(N-4), Trp(N-86), or Gln(N-6) of the I7L protein, wherein position N corresponds to the catalytic cysteine of I7L. Additionally, the interacting group of I7L may comprise at least one of Gly(N+1), Leu(N-5), Ser(N-88), Trp(N-160), Asp(N-134), Asn(N-157), Ser(N-155), Met(N-133), Ser(N-2), Glu(N-1), Leu(N-89), Leu(N-151), Asn(N-129), Met(N-159), Phe(N-92), Ile(N-125) or Met(N-95), wherein position N corresponds to the catalytic cysteine of I7L.

The computer model may further employ a modified protein. Thus, the pharmacophore may be evaluated for its interaction with a modified I7L protein, or portion thereof, wherein the I7L comprises at least one of an amino acid substitution, an amino acid deletion, or an amino acid insertion. In one embodiment, the I7L amino acids used to determine the nature of the association between the pharmacophore and the I7L protein, or a portion thereof, comprise at least one of wild-type or altered amino acid in the I7L protein corresponding to positions 168, 169, 171, 173, 177, 194, 195, 199, 203, 233, 236, 239, 240, 241, 242, 248, 258, 322, 323, 324, 326, 327, 328, or 329 of the wild-type VV I7L protein.

In yet another embodiment, the present invention comprises compounds that interact with at least one atom or molecular group of the I7L protein. In an embodiment, such compounds bind to the catalytic domain and/or catalytic site of I7L. In yet another embodiment, the compounds include molecules that interact with residues known to be in the ligand binding domain and/or ligand binding site. In yet a further embodiment, the compound comprises TTP-A or TTP-B.

The interaction between the compound and I7L may comprise an *in silico* interaction defined by a computer model of the structure of the compound and a computer model of the I7L protein, or a portion thereof. Thus, the present invention may also comprise a compound identified by docking a computer representation of the compound with a computer representation of a structure of I7L, or a portion thereof, as defined by Table 2. Where I7L is defined by the coordinates of Table 2, the spatial arrangement of atoms within the compound may comprise the atomic coordinates for at least one of the docking modes as defined in Table 3. In another example embodiment, the spatial arrangement of atoms within the compound comprises the atomic coordinates for at least one of the docking modes as defined in Table 4.

The nature of the interaction between the compound and the protein of interest may be defined in terms of the atomic interaction between the compound and the protein of interest. In an embodiment, the atomic interaction between a potential modulator compound and the I7L protein, or a portion thereof, comprises at least one atomic interaction selected from the group consisting of charge, electrostatic, hydrogen bond, and hydrophobic. Alternatively, the atomic interaction between a potential modulator compound and the I7L protein, or portion thereof, may comprise at least two hydrogen bond atomic interactions, at least two hydrophobic atomic interactions, and at least one of a charge or electrostatic interaction. Or, the atomic interaction between a potential modulator compound and the I7L protein, or a portion thereof, may comprise at least three hydrogen bond atomic interactions, at least three hydrophobic atomic interactions, and at least one of a charge or electrostatic interaction. For example, for I7L, the atomic interactions between the compound and I7L may comprise at least one of the atomic interactions described in Table 5. Or, the atomic interactions between the compound and I7L may comprise at least one of the atomic interactions described in Table 6.

The present invention also comprises pharmaceutical compositions comprising compounds able to modify the activity of a protein of interest. In one embodiment, the protein of interest may comprise I7L. Also, the pharmaceutical compositions may comprise anti-viral activity. In one embodiment, the present invention may comprise a pharmaceutical composition comprising a compound identified by docking a computer representation of the compound with a computer representation of a three-dimensional structure of I7L, or a portion thereof. The structure of I7L or a portion

thereof, may comprise at least some of the atomic coordinates as defined by Table 2. Also, the three dimensional structure of the compound used in the pharmaceutical composition may comprise at least some of the atomic coordinates of at least one of the docking modes as defined in Table 3. Or, the three dimensional structure of the compound used in the pharmaceutical composition may comprise at least some of the atomic coordinates of at least one of the docking modes as defined in Table 4.

The nature of the interaction between the compound of the pharmaceutical composition and the protein of interest may be defined in terms of the atomic interaction between the compound and the protein of interest. In an embodiment, the atomic interaction between a potential modulator compound and the I7L protein, or a portion thereof, comprises at least one atomic interaction selected from the group consisting of charge, electrostatic, hydrogen bond, and hydrophobic. Alternatively, the atomic interaction between a potential modulator compound and the I7L protein, or portion thereof, may comprise at least two hydrogen bond atomic interactions, at least two hydrophobic atomic interactions, and at least one of a charge or electrostatic interaction. Or, the atomic interaction between a potential modulator compound and the I7L protein, or a portion thereof, may comprise at least three hydrogen bond atomic interactions, at least three hydrophobic atomic interactions, and at least one of a charge or electrostatic interaction. For example, for I7L, the atomic interactions between the compound able to modify I7L and the I7L protein may comprise at least one of the atomic interactions described in Table 5. Or, the atomic interactions between the compound able to modify I7L and the I7L protein may comprise at least one of the atomic interactions described in Table 6.

The compound may be defined by its ability to interact with amino acids in the protein of interest that are important for catalytic activity and/or substrate binding. In one embodiment for an I7L modulating compound, the interacting atom or molecular group for I7L may comprise the catalytic cysteine of I7L. In one embodiment, the atomic interactions with the catalytic cysteine may comprise a charge or electrostatic interaction. Or, the interacting atom or molecular group for I7L may comprise at least one of amino acids Cys328, His241, Asp248, Asp258, of I7L. Or, the interacting atom or molecular group for I7L may comprise at least one of amino acids Leu324, Trp242, and Gln322 of I7L. Additionally, or alternatively, the interacting atom or molecular group of I7L may comprise at least one of Gly329, Leu323, Ser240, Trp168, Asp194, Asn171, Ser173, Gln 322, Met195, Ser326, Glu327, Leu239,

Leu177, Asn199, Met169, Phe236, Ile203, or Met233 of the I7L protein. In one embodiment, the I7L, or a portion thereof, is VV I7L.

Depending on the source of the protein used to generate a three-dimensional structure, there may be some variability in the absolute positioning of each amino acid. Still, due to the high homology maintained among I7L proteins from various sources at least in the catalytic triad region, it is to be expected that the relative positions of conserved amino acids may be maintained. For example, for I7L, the interacting group(s) used to determine the atomic interactions between the compound and I7L protein may comprise Cys(N), wherein position N corresponds to the catalytic cysteine of I7L. Additionally, the interacting group(s) may comprise at least one of His(N-87), Asp(N-80), Asp(N-70), of the I7L protein, wherein position N corresponds to the catalytic cysteine of I7L. Additionally, the interacting group(s) may comprise at least one of Leu(N-4), Trp(N-86), or Gln(N-6) of the I7L protein, wherein position N corresponds to the catalytic cysteine of I7L. Additionally, the interacting group of I7L may comprise at least one of Gly(N+1), Leu(N-5), Ser(N-88), Trp(N-160), Asp(N-134), Asn(N-157), Ser(N-155), Met(N-133), Ser(N-2), Glu(N-1), Leu(N-89), Leu(N-151), Asn(N-129), Met(N-159), Phe(N-92), Ile(N-125) or Met(N-95), wherein position N corresponds to the catalytic cysteine of I7L.

The compound may also be evaluated for its interaction with a modified I7L protein, or portion thereof, wherein the I7L comprises at least one of an amino acid substitution, an amino acid deletion, or an amino acid insertion. In one embodiment, the I7L amino acids used to determine the nature of the association between the compound and the I7L protein, or a portion thereof, comprise at least one of wild-type or altered amino acid in the I7L protein corresponding to positions 168, 169, 171, 173, 177, 194, 195, 199, 203, 233, 236, 239, 240, 241, 242, 248, 258, 322, 323, 324, 326, 327, 328, or 329 of the wild-type VV I7L protein.

The pharmaceutical composition may comprise the compound present in a therapeutically effective amount. In one embodiment, a therapeutically effective amount may comprise an amount sufficient to reduce a viral load in a subject. The dosage used for the pharmaceutical compositions of the present invention may vary depending on the specific compound being used, as well as the methods of administration. In one embodiment, a therapeutically effective amount may comprise a dose in a range from about 0.01 to 1,000 mg of active compound per kg body weight per day.

The pharmaceutical compositions and compounds of the present invention may be used to treat or prevent a variety of viral infections. The virus may comprise an orthopox virus, such as smallpox virrus, vaccinia virus, monkeypox virus, mulluscipox virus, cowpox virus, camelpox virus, variola major virus, variola minor virus, ectromelia virus, sheeppox virus, lumpy skin virus, Yaba-like virus, swinepox virus, rabbit fibroma virus, myxoma virus, fowlpox virus, canarypox virus, or amsacta moorei virus. In one example embodiment, the virus is smallpox virus. Also, additional anti-viral agents may be employed.

The present invention also comprises a method of conducting a drug-discovery business. The method may comprise the step of generating a three-dimensional structural model of a target molecule of interest on a computer. Also, the method may comprise generating a three-dimensional structural model of a potential modulator compound of the target molecule on a computer, and docking the model for the potential modulator compound to with the target molecule so as to minimize the free energy of the interaction between the target molecule and the potential modulator. In this way, a modulator compound that may interact with the target may be identified. The method may also include the subsequent steps of providing a modified structure for the modulator compound of interest, and assessing whether the modified structure has a lower free energy of interaction with the target than the original structure for the modulator compound.

The method may further include evaluating at least some of the potential modulator compounds identified by *in silico* screening in a biological assay. Once compounds initially identified by the *in silico* assay are corroborated by a biological assay, animal studies may be used for detailed therapeutic profiling, and pharmaceutical compositions may then be developed. Or, additional in silico assays may be conducted on compounds that appear to be promising based on the biological data.

In another embodiment, the present invention comprises treatment of orthopox viral infections using compounds identified by the methods and systems of the present invention and pharmaceutical compositions comprising such compounds. The virus may comprise smallpox virrus, vaccinia virus, monkeypox virus, mulluscipox virus, cowpox virus, camelpox virus, variola major virus, variola minor virus, ectromelia virus, sheeppox virus, lumpy skin virus, Yaba-like virus, swinepox virus, rabbit

fibroma virus, myxoma virus, fowlpox virus, canarypox virus, or amsacta moorei virus. In one example embodiment, the virus is smallpox virus.

The compound may comprise a small organic compound. In one example embodiment, the compound may comprise TTP-A, or a salt or prodrug thereof, as defined herein. Or, the compound may comprise TTP-B, or a salt or prodrug thereof, as defined herein.

Structural Modeling of I7L

Embodiments of the present invention comprise computer modeling methods and systems to identify and optimize specific small molecules that bind to, and thus, are able to modulate the activity of, a particular target protein. In one embodiment, the protein is I7L. Also provided by the present invention are compounds identified using the modeling methods described herein.

Thus, in one embodiment, the present invention provides a method of generating a three-dimensional model of a protein, or a portion thereof. The method may comprise the steps of providing an amino acid sequence of the protein of interest and comparing the amino acid sequence of the protein of interest to the amino acid sequences of other proteins to identify a second protein for which a three-dimensional structure has been defined, and that has a predetermined level of sequence identity to the protein of interest. Once a second protein having a known structure has been identified, the method may include the step of aligning conserved residues from the protein of interest with conserved residues from the second protein. Next, the sequence for the protein of interest may be threaded along the three-dimensional structure of the second protein such that the position of at least two conserved residues from both proteins are aligned. The conserved residues from the first protein and the second protein may comprise residues that are essential for protein function.

Thus, as a first step, a three-dimensional model of the protein of interest may be generated. To generate a three dimensional model of a protein of interest, a sequence comparison to proteins with experimentally determined three-dimensional structures may be performed. The protein aligned with the protein of interest may comprise a protein having a similar sequence to the protein of interest. The level of sequence identity may range from at least 5% sequence identity, to more than 10% sequence identity, to more than 20% sequence identity.

The protein aligned with the protein of interest may not necessarily be functionally related to the protein of interest. Or, the protein aligned with the protein

of interest may comprise a protein having a similar function to the protein of interest. In this way, conserved residues that have similar functions in the two proteins may be aligned.

In one embodiment, the protein of interest may comprise I7L. In performing structural modeling for I7L, a high sequence identity for vaccinia virus (VV) I7L is found with the C-terminal domain of another cysteine protease, Ubiquitin-like protease 1 (ULP1). ULP1 protease consists of 221 amino acids, and exhibits a 22% sequence identity with I7L. ULP1 may be used as a template for building the three dimensional model of I7L.

To develop a three dimensional structure for I7L, TTPredict™ site search algorithms may be used to identify the ligand binding site of I7L based on the location of active site residues His241, Asp248, and Cys328, that are known to be essential for I7L activity. Also, TTPredict™ algorithms may be used to identify known I7L-homologous sequences using BLAST searches on protein sequence databases. TTPredict™ algorithms may also be used to access a number of publicly available and vendor supplied fold recognition programs to analyze I7L sequence folds (e.g., MSI suite of programs, TTPGene). Such sequence comparisons reveal that, as compared to other proteins with known 3D structures, the C-terminus domain of ULP1 (wwPDB Protein Data Bank Archive: PDB code:1EUV) has a high structural homology to I7L sequence. The ligand binding domain of the I7L sequence (amino acids 110-423) may be mapped onto residues from the C-terminus of ULP1 protease domain using 3DPSM and the Homology modeling suites within the Accelrys suite of programs (San Diego, CA). Despite having only a 22% sequence identity with I7L, the 3D structure of ULP1 may be used as a threading template to generate a 3D model for the I7L query sequence.

The threading approach may reveal distantly homologous proteins that share the same folding structure, but that do not comprise a high amount of sequence similarity. Rather than relying only on sequence alignment, the fold recognition method may blend the sequence-to-structure fitness with other structural characteristics, such as sequence similarity and predicted secondary structures, to find conserved residues that appear in both the template protein of interest (e.g., I7L) as well as any query sequences, and overlay both sequences, maintaining alignment of the conserved residues. Next, the threading program may match the query sequence on the three-dimensional structure of the template using conserved residues of the

query protein as the hang points. The resulting model may then be cleaned-up using standard energy minimization and molecular dynamics techniques. In one embodiment, the conserved residues used as hang points may need to be determined *a priori*. FIG. 1 shows the results of the analysis for I7L and ULP1, wherein the hang point residues for ULP1 (His514, Cys580, and Trp448) are aligned with analogous and conserved I7L residues (His241, Cys328, Trp168) to generate a three-dimensional structure for I7L.

The present invention also comprises a computer-generated molecular model for I7L. For example, FIG. 2 shows a ribbon representation of I7L ligand binding domain based on alignment of the I7L protein sequence with ULP1 to generate a three-dimensional structure for the ligand binding domain of I7L. The model may comprise the catalytic site required for I7L-mediated cleavage of substrate proteins. The model may further include the ligand binding site for antiviral small molecule ligands. The predicted active site residues for I7L may include those residues that form the catalytic site, or residues that form the ligand binding site, or residues that participate in neighboring interactions required to maintain the structure of the ligand binding domain and/or the chemical functions required for the catalytic site. In FIG. 2, amino acid residues that comprise at least a part of the substrate binding pocket are labeled. Also, the predicted ligand binding site is shown within the oval shaped area.

The model may be further refined once the initial structural coordinates are defined. Thus, specific aspects of the model, such as the catalytic site and/or a ligand binding site, may be refined to incorporate the structures of substrates or ligands that may be bound at that site. I7L has two domains, a cyteine protease domain and a DNA regulatory domain. In the present invention, the cysteine protease domain was modeled, and is referred to as the ligand binding domain. The ligand binding domain thus includes the catalytic site, where substrate polypeptides are hydrolyzed, and a ligand binding site, where small molecule ligands bind. For example, FIG. 3 shows a detailed map of the I7L ligand binding site. It can be seen that Gln 322, Cys 328 (the catalytic cysteine), Trp168, Asn171, Asp194, Leu239, His241 and Asp258 line the ligand-binding site to some extent (FIG. 3). As shown in FIG. 3, the catalytic cysteine residue, Cys328, is located deep in the pocket. The Trp168 side chain protects the Cys328 residue from the solvent. Table 1 lists residues that may comprise the I7L ligand binding and catalytic site. In an embodiment, a more detailed

view, showing potential intramolecular interactions such as hydrophobic bonds, salt bridges and Van Der Waals interactions may be generated.

Table 1 Predicted catalytic site residues of I7L
Cys328, Leu 323, **Leu324**, **His241**, Ser240, Trp168, Asp194, Asp258, **Trp242**, Asp248, Asn171, Ser173, **Gln 322**, Met195, Cys237, Leu239, Leu177, Met233, Ile332, Ile174, Lys175, Leu198, Phe234, Gln192, Ile161

The structure of I7L may be defined by a graphic two-dimensional figure of a three-dimensional model as shown in FIGS. 1-3. The representations shown in FIG. 1-3 may also be viewed on a computer screen. When visualized on the computer, the models may be rotated to provide multiple views. For example, the viewer may rotate the model so as to provide a view that is rotated to the right or the left of the views shown in FIGS. 1-3. Or, the models depicted as FIG. 1-3 may be used to form a physical model.

Additionally, the structure of the I7L protein, or a portion thereof, may be defined by the atomic coordinates in three dimensional space. Table 2 provides the three-dimensional atomic coordinates for the I7L ligand binding domain, wherein the position of each atom is defined by a unique x, y, and z coordinate in three dimensional space. Shown in Table 2, is the identity of the atom (column 3), the amino acid and residue number (cols. 4 and 5), and the actual coordinates for each atom in x, y, and z dimensions (cols. 6, 7, and 8, respectively. As described herein, a data set of structural coordinates defines the three dimensional structure of a molecule or molecules. Structural coordinates can be slightly modified and still render nearly identical three dimensional structures. A measure of a unique set of structural coordinates is the root-mean-square deviation of the resulting structure. In alternate embodiments, structural coordinates that render three dimensional structures that deviate from one another by a root-mean-square deviation of less than 3.0 angstroms, or less than 2.0 angstroms, or less than 0.5 angstroms, or less than 0.3 angstroms, may be viewed by a person of ordinary skill in the art as identical or equivalent.

In Silico Screening Of Putative I7L Modulators

The present invention further provides methods to dock compounds of interest, such as putative therapeutic agents, into the structure of the modeled protein to determine whether such putative therapeutic agents may interact with the protein. In one embodiment, the protein of interest is I7L protein, and the putative therapeutic agents are putative modulator compounds. For example, the modulator compounds may act as anti-viral agents. Thus, the putative therapeutic agents may bind to the ligand binding site and/or catalytic site to modify I7L activity.

To generate a three dimensional model of a potential modulator compound of interest, or a plurality of potential modulator compounds, a database of *in silico* structures for potential modulator compounds of interest, such as provided by TTProbes™, may be used. Once the three-dimensional structures of the modulator compounds of interest have been generated, the compounds may be docked into the ligand binding site of the protein of interest.

For example, in one embodiment, the site tested for interaction with potential modulator compounds being tested for anti-viral activity may comprise the ligand binding domain of I7L as described by the three-dimensional model. The amino acids which are assessed for interaction with the test compounds may comprise amino acids involved in catalysis, such as Cys328 of the VV I7L protein. Many of the residues relevant for I7L catalytic activity appear to be located in the immediate vicinity of the ligand binding site as defined by the three-dimensional model of the present invention. For example, in one embodiment, amino acids important for catatlytic activity are included within a 3 angstrom radius of the residues in Table 1. Additionally or alternatively, the amino acids important for catatlytic activity are included within a 3 angstrom radius of the catalytic cysteine, histindine, and/or aspartate in the catalytic triad. For example, there are several conserved amino acids, including Ser240, His 241, Trp168, Trp 242, Asp 248, Asp 258, Gln 322, Cys 328, and Gly 329, that may be relevant for I7L catalytic activity. Also, compounds may be specifically tested for their ability to interact *in silico* with Cys328 as the catalytic cysteine. For I7L, the amino acids assessed for putative interactions with test compounds may include at least some of the amino acids listed in Table 1. In one example embodiment, the amino acids tested for interaction with the test compound may comprise His 241, Trp 242, Asp 248, Asp 258, Gln 322, Cys 328, Gly 329,

Leu324, Leu323, Ser240, Trp168, Asp194, Asn171, Ser173, Met195, Ser326, Glu327, Leu239, Leu177, Asn199, Met169, Phe236, Ile203, and/or Met233 of the vaccinia virus I7L.

The putative therapeutic agents may comprise a variety of compounds. In one embodiment, the putative therapeutic agent may comprise a peptide or a peptidomimetic. Or, the putative therapeutic agent may comprise an antibody. Alternatively, the putative therapeutic agent may comprise a small organic compound.

FIG. 4 shows a docking mode of a small organic compound with the I7L ligand binding domain. The compound shown docked in the ligand binding domain of I7L is 3-hydroxy-naphthalene-2-carboxylic acid [2-(2-methoxy-4'-nitro-biphenyl-3-yl)-ethyl]-amide (TTP-A). TTP-A is shown as a meshed surface. It can be seen that one end of TTP-A makes contact with the catalytic cysteine (Cys328) and histidine (His241) residues and at least some of the other catalytic residues listed in Table 1. A similar compound, 3-(3'-chloro-4'-fluoro-biphenyl-4-yl)-2-[(4-hydroxy-4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-propionic acid methyl ester, (TTP-B), and other similar active analogs, make canonical contacts with active site residues of I7L protease.

The structure of a putative ligand may be provided as a three-dimensional space-filling model, as a rotatable model on a computer screen, or as atomic coordinates in three-dimensional space. In one embodiment, the compounds that dock into the ligand binding site with a negative free energy are considered to be favorable. In alternative embodiments, a compound having an free energy of interaction with I7L (or another molecule of interest) of less than –2 kcal/mol, or less than –5 kcal/mol, or less than –10 kcal/mole, are considered to provide favorable binding to the protein of interest. For example, Tables 3 and 4 provides the coordinates for several computed low-energy docking modes for TTP-A and TTP-B, respectively. For TTP-A, the energy of interaction is about –11.24 kcal for all five docking modes. For TTP-B, the energy of interaction ranges between –8.81 kcal/mol to about –10.68 kcal/mol for the five low-energy docking modes.

Thus, the three-dimensional coordinates as listed in Tables 3 and 4 provide the low energy structures of TTP-A and TTP-B, respectively, as each compound interacts with I7L. The low-energy docking modes for TTP-A as provided in Table 3, and for TTP-B as provided in Table 4, may favor interactions with at least some of the I7L residues listed in Table 1. In Tables 3 and 4, from the left, the second column

identifies atom number, the third column identifies atom type, the fifth column identifies the docking mode (i.e., 1-5) the sixth column identifies the x coordinates, the seventh column identifies y coordinates, and the eighth column identifies the z coordinates.

In one example embodiment, TTP-A, TTP-B, and their derivatives, bind to the same binding surface of the I7L model. For example, in the predicted docking with I7L, active therapeutic compounds will make favorable contacts with at least some of the residues shown in Table 1. As the residues identified in Table 1 appear to be required for catalytic activity, it may be of importance that the putative therapeutic agent recognizes the binding surface that is described in Table 2 and at least some of the residues as described in Table 1 to provide the potential inhibit the cysteine protease activity of I7L.

The molecular model may be further corroborated by studies of drug-resistant mutants. For example, in one embodiment, a drug-resistant virus may be isolated by passaging of the virus in the presence of the drug of interest. For example, a vaccinia virus passaged in the presence of TTP-A may, after several passages, result in the emergence of a viral strain that exhibits resistance to the inhibitory effects of TTP-A. The resistant virus may be isolated, and the I7L gene sequenced to determine whether resistance is due to a change of the I7L protein, such that the TTP-A is no longer as effective therapeutically. In one embodiment, passaging of the virus in the presence of TTP-A may result in a mutation of the I7L protein. For example, passage of vaccinia virus in the presence of TTP-A may result in mutations in certain positions of the protein. In alternate embodiments, there may be a Y to C mutation at position 104 of the I7L protein, and an L to M mutation at 324 of the I7L protein. FIG. 5 shows a model of the I7L active site showing that the position of Leu324 is in close proximity to the catalytic cysteine, Cys328.

Tables 5 and 6, list the nature of several atomic interactions for TTP-A and TTP-B, respectively, with atoms in the I7L protein. Thus, Tables 5 and 6, identify groups on I7L, as defined by Table 2, that interact with the designated atom on TTP-A or TTP-B, as defined by the first docking mode of either Table 3 or Table 4, respectively. By comparing the relative coordinates of the I7L residues to the coordinates of the atoms in the first docking modes for TTP-A and TTP-B, the distance between the atoms and the type of interaction may be determined. The

structures of TTP-A and TTP-B, with the numbering of atoms for each molecule as used in Tables 5 and 6, are shown in FIG. 6.

The molecular model may be used in a computational assay by which virtual ligands are inserted into the active site to identify those agents having the highest potential to bind to, and/or modify, the I7L activity. In a further embodiment, the compounds identified by molecular modeling are tested in a biological assay. For example, compounds may be evaluated to determine whether the compound displays cytotoxic effects on uninfected cells. Additionally, the compound may be evaluated to determine the amount of compound that exhibits an inhibition of cytopathic effect (CPE) of the virus.

The results of the determination of cytotoxicity may be compared to the effectiveness of the compound as an anti-viral agent, to determine the therapeutic index (TI) of the compound. The 50% inhibitory concentrations (IC50), measured as the concentration of the compound that results in inhibition of the viral cytopathic effect (CPE) for 50% of treated cells, and the 50% toxicity concentration, measured as the concentration of the compound at which 50% of uninfected cells display signs of cytotoxicity (TC50), may be compared, and the therapeutic index calculated as the value of TC50 divided by IC50.

The results of the biological assay may provide further data which can be used in the next round of molecular modeling. For example, compounds that display a large therapeutic index may be further modified *in silico* to attempt to improve the effectiveness of the compound and then reevaluated by a biological assay. The process may be repeated until a compound maximal TI is identified. In addition, the compound may be further developed by animal testing and formulation of an appropriate pharmaceutical composition.

In addition to a cell culture assay, a molecular assay of the effectiveness of the compounds identified by *in silico* screening may be performed. For example, the ability of a candidate compound such as TTP-A may be evaluated by determining whether the compound inhibits proteolysis of a I7L substrate, such as the P4b precursor protein, by I7L. Such molecular assays may provide evidence that the compound of interest is targeting the protein of interest to inhibit catalysis. If inhibition of cleavage of the substrate is not observed, it may indicate that the compound identified by *in silico* screening is acting at a different point of the viral formative and/or morphogenic cycle.

A schematic of a method used to develop anti-viral agents is shown in FIG. 7. Thus, the method may include a first stage 100 of developing a three-dimensional model of a protein or polypeptide of interest (e.g., viral I7L). As described herein, the method may comprise providing the amino acid sequence for the protein or polypeptide of interest 110. The sequence of the protein or polypeptide of interest may then be compared to amino acid sequences available in protein sequence databases 120 to identify proteins or polypeptides that have a known structure, and that may be homologous in structure to the protein or polypeptide of interest 130. If a second polypeptide or protein of known structure that has a sequence that includes regions of identity to the protein or polypeptide of interest is identified, the second protein may be used to align conserved residues from the second protein or polypeptide with the first protein or polypeptide of interest 140. The aligned residues (hang-points) may then be used as anchors as the first polypeptide or protein of interest is threaded along the structure of the second protein or polypeptide of interest to construct a three-dimensional model of the first polypeptide or protein of interest 150.

Once a three-dimensional model of the protein or polypeptide of interest has been constructed, it may be used in an *in silico* assay for screening a plurality of compounds 200. The *in slico* assay may comprise generating a library of three-dimensional structures for potential therapeutic agents 210. For example, in one embodiment a library of small high information density organic molecules (i.e., a library, wherein each small molecule within the library contains at least one functional group of interest) may be prepared. Such a library is provided by TTProbes™ (TransTech Pharma., Inc., High Point, NC) which is a set of more than 51,000 phramcophorically diverse molecules of high information density. The *in silico* probes may then be docked into the three-dimensional structure of the protein or polypeptide of interest as described herein to determine the atomic interactions between the protein/polypeptide and the compound 220. Optionally, the compound may also be modified by adding or removing molecular fragments from the compound 230, and then the modified compounds docked into the three-dimensional structure of the protein or polypeptide of interest 240 to determine how the changes to the structure of the compound may affect the interaction of the compound with the protein/polypeptide. Such molecular alterations may be made until there is no longer

an apparent improvement in the ability of the compound to interact with the polypeptide/protein of interest. For example, for I7L, and using the TTProbes™ in silico library, over 3,000 candidate potential I7L modulators were identified. The method may include the option 299 of developing the compounds identified by *in silico* screening, or, performing further testing of the compounds by a biological assay.

Thus, still referring to FIG. 7, the putative therapeutic agents (i.e., potential modulator compounds) identified by *in silico* screening may then be evaluated by other types of assays for biological activity 300. For example, a putative receptor ligand may be evaluated using a binding assay. For putative anti-viral agents, the compounds may be evaluated to determine whether they inhibit viral growth and propagation 310. Also, the compounds may be evaluated to determine whether they are toxic to uninfected cells 320. For example, results of such biological tests for I7L indicate that of the 3,460 compounds identified by in silico screening, 136 inhibit viral replication and are not toxic. Additionally, compounds may be evaluated to determine if they inhibit enzymatic activity of the protein of interest 330. For example, for I7L, the cleavage of an I7L substrate, P4b, may be measured by electrophoresis of proteins from cell lysates from vaccinia virus-infected cells on SDS-PAGE gels. Treatment with TTP-A of viral infected cells results in inhibition of the cleavage of the P4b protein, as expected if TTP-A inhibits the catalytic activity of I7L (Byrd, C.M., et al., 2004, *J. Virol.* **78**:12147-12156).

The results of the biological testing may indicate that certain structures are of interest as displaying efficacy as anti-viral agents. Thus, there is the option 399 to test at least some of these structures in additional *in silico* assays to determine if additional chemical modifications may be made to the structures to improve the therapeutic effects. Or, the compounds may then considered to be optimized, and thus, comprise lead compounds for additional animal studies and the like 400.

Therapeutics

The invention further provides pharmaceutical compositions comprising the antiviral active compounds of the invention. The pharmaceutical compositions containing a compound of the invention may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous, or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any known method,

and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically-acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in U.S. Patent Nos. 4,356,108; 4,166,452; and 4,265,874, to form osmotic therapeutic tablets for controlled release.

Formulations for oral use may also be presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or a soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions may contain the active compounds in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide such as lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyl-eneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also

contain one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active compound in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring, and coloring agents may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example a liquid paraffin, or a mixture thereof. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Also, oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as a liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may also be in the form of a sterile injectible aqueous or oleaginous suspension. This suspension may be formulated according to the known methods using suitable dispersing or wetting agents and suspending agents described above. The sterile injectible preparation may also be a sterile injectible solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic

sodium chloride solution. In addition, sterile, fixed oils are conveniently employed as solvent or suspending medium. For this purpose, any bland fixed oil may be employed using synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectibles.

The compositions may also be in the form of suppositories for rectal administration of the compounds of the invention. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will thus melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols, for example.

For topical use, as for example for treatment of molluscipox virus, creams, ointments, jellies, solutions of suspensions, etc., containing the compounds of the invention are contemplated. For the purpose of this application, topical applications shall include mouthwashes and gargles.

The compounds of the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes may be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Also provided by the present invention are prodrugs of the invention.

Pharmaceutically acceptable salts of the compounds of the present invention, where a basic or acidic group is present in the structure, are also included within the scope of the invention. The term "pharmaceutically acceptable salts" refers to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid or by reacting the acid with a suitable organic or inorganic base. Representative salts include the following salts: Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium Edetate, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycollylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrocloride, Hydroxynaphthoate, Iodide, Isethionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Methanesulfonate, Methylbromide, Methylnitrate, Methylsulfate, Monopotassium Maleate, Mucate, Napsylate, Nitrate, N-methylglucamine, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Potassium, Salicylate,

Sodium, Stearate, Subacetate, Succinate, Tannate, Tartrate, Teoclate, Tosylate, Triethiodide, Trimethylammonium and Valerate. When an acidic substituent is present, such as–COOH, there can be formed the ammonium, morpholinium, sodium, potassium, barium, calcium salt, and the like, for use as the dosage form. When a basic group is present, such as amino or a basic heteroaryl radical, such as pyridyl, an acidic salt, such as hydrochloride, hydrobromide, phosphate, sulfate, trifluoroacetate, trichloroacetate, acetate, oxalate, male ate, private, malamute, succinct, citrate, tartarate, fumarate, mandelate, benzoate, cinnamate, methanesulfonate, ethanesulfonate, picrate and the like. Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of the invention; these form a further aspect of the invention.

In addition, some of the compounds identified as binding to, or modulating I7L, may form solvates with water or common organic solvents. Such solvates are also encompassed within the scope of the invention.

Thus, in another embodiment of the present invention, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound identified as binding to or modulating I7L, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents. In an embodiment of the pharmaceutical composition, the compound identified as binding to or modulating I7L, is an inhibitor of orthopox viruses, including smallpox virus.

In another embodiment, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of the compound identified as binding to or modulating I7L, and one or more pharmaceutically acceptable carriers, excipients, or diluents, wherein said pharmaceutical composition is used to replace or supplement compounds that posses antiviral activity.

In another embodiment, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of the compound identified as binding to, or modulating I7L, and one or more pharmaceutically acceptable carriers, excipients, or diluents, and further comprising one or more additional therapeutic agents.

The compound identified as binding to, or modulating I7L, may administered in an amount sufficient to reduce the viral load in a subject. The compound identified as binding to, or modulating I7L, may be administered in the form of an oral dosage

or parenteral dosage unit. In alternative embodiments, the compound identified as binding to, or modulating I7L, is administered as a dose in a range from about 0.01 to 1,000 mg/kg of body weight per day, or as a dose in a range from about 0.1 to 100 mg/kg of body weight per day, or as a dose in a range from about 0.5 to 10 mg/kg of body weight per day. In another embodiment, the compound identified as binding to, or modulating I7L, is used to replace or supplement a compound that inhibits viruses.

The present invention also provides a prophylactic method for the inhibition of pox virus infection comprising administering to a subject in need thereof a compound identified as binding to, or modulating I7L, wherein the compound is administered to the subject as a pharmaceutical composition comprising a therapeutically effective amount of the compound and one or more pharmaceutically acceptable carriers, excipients, or diluents. The therapeutically effective amount of the compound identified as binding to, or modulating I7L may inhibit a pox virus. A therapeutically effective amount of the compound identified as binding to, or modulating I7L, may comprises an amount sufficient to achieve and maintain a sustained blood level that at least partially inhibit virus growth. In alternative embodiments, the sustained blood level of the compound identified as modulating I7L may comprise a concentration ranging from about 0.01 μM to 2 mM, or from about 1 μM to 300 μM, or from about 20 μM to about 100 μM. In another embodiment of the method, the pharmaceutical composition may further comprise one or more additional therapeutic agents.

The following is a non-exhaustive listing of adjuvants and additional therapeutic agents which may be utilized in combination with the Smallpox inhibitor of the present invention:

1. Analgesics: Aspirin
2. NSAIDs (Nonsteroidal anti-inflammatory drugs): Ibuprofen, Naproxen, Diclofenac
3. DMARDs (Disease-Modifying Antirheumatic drugs): Methotrexate, gold preparations, hydroxychloroquine, sulfasalazine
4. Biological Response Modifiers: Etanercept, Infliximab, Glucocorticoids

In a further preferred embodiment, the present invention provides a method of treating or preventing viral - mediated diseases, the method comprising administering to a subject in need thereof, a therapeutically effective amount of a compound

identified as binding to, or modulating I7L, alone or in combination with therapeutic agents selected from the group consisting of antibiotics, hormones, biologic response modifiers, analgesics, NSAIDs, DMARDs, or biological response modifiers. In one embodiment, the viral disease is caused by an orthopox virus, such as smallpox or other orthopox viruses.

For treatment of orthopox-mediated disease, or other viral disease, the compound identified as binding to, or modulating I7L, may be administered at a dosage level of from about 0.01 to 1000 mg/kg of the body weight of the subject being treated, or at a dosage range between 0.01 and 100 mg/kg, or at a dosage range between 0.5 to 10 mg/kg of body weight per day. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage will vary depending upon the host being treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain 1 mg to 2 grams of a compound identified as binding to, or modulating I7L, with an appropriate and convenient amount of carrier material, which may vary from about 5 to 95 percent of the total composition. Dosage unit forms may, in one embodiment, contain between from about 5 mg to about 500 mg of active ingredient. As is known in the art, the dosage may be individualized by the clinician based on the specific clinical condition of the subject being treated. Thus, it will be understood that the specific dosage level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

EXAMPLES

Example 1: Materials and Methods

Small organic compound stocks were prepared at a concentration of 10 mM in 100% dimethyl sulfoxide. The synthesis of TTP-A, TTP-B, and related compound is described in U.S. Patent Application 60/493,879, filed August 8, 2003 (TTP 2003-08). The disclosure of U.S. Patent Application 60/493,879, is hereby incorporated by reference in its entirety herein.

Cell lines used to measure toxicity of the compounds and antiviral effects included BSC40 cells, which are BSC1 African green monkey kidney cells adapted to grow at 40°C (Raczynski, P., et al., 1983, *Virology*, **128**:458-462). The vvGFP line is

a Western Reserve vaccinia virus with GGP in the thymidine kinase (TK) locus (Byrd, C.M., et al., 2004, *J. Virol.*, **78**:12147-12156).

Example 2: Computer Modeling

TransTech Pharma's Translational Technology™, described in U.S. Patent Applications 10/120,278, filed April 10, 2002, 10/410,965, filed April 10, 2003, and 10/411,568, filed April 10, 2003, each of which are incorporated by reference in their entireties, was used to model the I7L cysteine protease domain, to discover specific small molecule inhibitors, and to optimize I7L binding agents into preclinical drug candidates. TransTech Pharma's Translational Technology™ was designed and developed for rapid lead generation and optimization of drug candidates. The system consists of two subtechnologies: TTProbes™ and TTPredict™. TTProbes™ is a set of greater than 51,000 pharmacologically diverse molecules. TTPredict™, is a computer-based technology that automates high-throughput three-dimensional target model building, binding site identification, and conformational analysis. The TTPredict computer program is used to dock, score, and rank members of TTProbes set into a target binding site.

To develop putative anti-viral compounds, TTPredict™ was used to construct threading and homology models for I7L. I7L is known to be a member of the cysteine protease super-family and has 423 amino acid residues. Sequence comparison to proteins with experimentally determined three-dimensional (3D) structures showed that the highest sequence identity with vaccinia virus I7L is achieved by the Ubiquitin-like protease 1 (ULP1) protease C-terminal domain (PDB code:1EUV). Such sequence comparisons were performed using PDBBlast (available on-line at the NCBI web-site), 3DPSM (Bates, P.A., et al., 2001, Enhancement of Protein Modeling by Human Intervention in Applying the Automatic Programs 3D-JIGSAW and 3D-PSSM, *Proteins: Structure, Function and Genetics*, Suppl **5**:39-46), MOE (MOE, Chemical Computing Group) (available on-line at the Chemical Computing Group web-site) and SeqFold within the MSI suite of programs (Accelrys Inc., San Diego, CA). ULP1 is also a member of the cysteine protease super-family and has 221 amino acids in the catalytic domain. Based on the sequence comparison, it was determined that ULP1 has a 22% sequence identity with I7L. The 303-residue ligand binding domain of I7L sequence (amino acids 110-423) was mapped onto 301 residues from the C-terminus of ULP1 protease domain using 3DPSM and the Homology modeling suites within the Accelrys suite of programs (San Diego, CA).

The sequence of the I7L polypeptide comprising the three-dimensional model of Table 2 s provided herein as SEQ ID NO. 1. Despite having only a 22% sequence identity with I7L, the 3D structure of ULP1 was successfully used as a threading template to generate a 3D model for the I7L query sequence.

I7L and ULP1 sequences were aligned in a manner that maintains perfect alignment of their conserved residues. In particular, their catalytic Cys – His – Trp combination from the ULP1 catalytic domain were used as hang points to anchor I7L sequence on the 3D structure of ULP1. The threading protocols identified a Cys/His/Trp hang points triplets in I7L to be residues His241/Cys328/Trp168. The corresponding triplets in ULP1 protease were identified to be His514/Cys580/Trp448. Following threading, the Cα atoms of I7L residues were placed at the corresponding Cα positions of UlP1 using Homology module (Accelrys, San Diego, CA). The resulting structure was energy minimized using Discover (Accelrys) to generate I7L structure that served as a model. The hang point residues are shown in FIG. 1, which also shows the locations of these residues in I7L and ULP1 protease.

Site search algorithms were used to identify the catalytic site of I7L. The resulting model agrees well with previous structural and biochemical studies for cysteine proteases. For example, several conserved amino acids including His241, Trp242, Asp248, Asp258, Gln322, Cys328, and Gly329, have been experimentally shown to be relevant for I7L catalytic activity. In the three-dimensional model generated for I7L, it was found that most of these residues are located in the immediate vicinity of the catalytic site (FIG. 2).

Table 2 provides the coordinates for the three dimensional structure for I7L developed using the methods of the present invention. In this table, from the left, the second column identifies atom number; the third identifies atom type; the fourth column identifies amino acid type; the fifth column identifies the residue number; the sixth column identifies the x coordinates, the seventh column identifies y coordinates; and the eighth column identifies the z coordinates. Also, shown in the ninth column the occupancy, and the last column of Table 2 provides the temperature factor or B factor. The B factor can be defined as:

$$B=8^* \Pi^*2 (<ud2> + <us2>);$$

where <ud2>, is the dynamic variability, and contains information on atom variability in an exposed versus buried state, and the temperature dependence on variation; and

<us2>, is the static variability, and contains information relating to unresolved occupancy, altered electron density, and crystal disorder. The occupancy and B factor fields are not required for the analyses described herein, however.

Example 3 In Silico Assay

TTProbes were docked into the ligand binding site (FIG. 3). The fit of every docked probe was computed using several scoring functions. High-scoring probes were identified, and the highest ranking TTProbes were submitted for *in vivo* screening.

For I7L, the amino acid residues His 241, Trp 242, Asp 248, Asp 258, Gln 322, Cys 328, Gly 329, Leu324, Leu323, Ser240, Trp168, Asp194, Asn171, Ser173, Met195, Ser326, Glu327, Leu239, Leu177, and/or Met233 are predicted to be important in binding to substrates. In Table 1, additional amino acid residues that potentially bind to the substrate protein as well as that can bind to small molecule ligands are listed. Amino acids shown in bold font in the Table 1 are residues that appear to be critical in binding to small molecule ligands. Amino acid residues that are not in bold also constitute the ligand binding site. For clarity, only a few amino acid residues are identified in FIGS. 1-5, which show the ligand binding site.

The 51,389 probe molecules comprising TTProbes™ database were then docked into the catalytic site. The fit of every docked probe was computed using several scoring functions. Prior to docking the probes into I7L active site, 1000 low energy conformers per probe were generated using Monte-Carlo procedures. TTPredict™ was used to dock *in silico* every conformer into the predicted site of I7L. Individual or consensus scoring functions including LUDI (Böhm, H.J., 1994, *J. Comp. Aided Molec. Design*, 8:243-256), PLP (Gehlhaar et al, 1995, *Chem. Bio.*, 2:317-324), DOCK (Meng, E.C., et al., 1992, J. *Comp. Chem.* 13:505-524), LigFit, (Accelrys, San Diego, CA), JAIN (Jain, A.N., 1996, *J. Comp. Aided Molec. Design* 10:427-440), and Poisson-Boltzmann (Honig, B. et al., 1995, *Science*, 268:1144-9) were used. High consensus scoring probes were identified and the 3,480 highest-ranking probes were submitted for *in vitro* (i.e., biological) testing. This process led to the identification of several lead compounds including, but not limited to, TTP-A and TTP-B.

Tables 3 and 4 provide the coordinates for the computed low-energy docking modes for TTP-A and TTP-B, respectively. Thus, the three-dimensional coordinates as listed in Tables 3 and 4 provide structures for TTP-A and TTP-B as each

compound interacts with I7L. The docking modes as provided in Tables 2 and 3 are presented in order of increasing energy, where a low energy associated with docking the compound into the I7L protein is thermodynamically more favorable than a high energy of interaction. The low-energy docking modes for TTP-A and TTP-B as shown in Tables 3 and 4 favor interactions with I7L residues listed in Table 1. In Tables 3 and 4, from the left, the second column identifies atom number, the third column identifies atom type, the fourth column identifies molecule name, the sixth column identifies the x coordinates, the seventh column identifies y coordinates and the eighth column identifies the z coordinates. The last column of Tables 3 and 4 provides the temperature (B) factor.

Biological Assay

The following assay methods may be utilized to identify compounds that are effective in showing antiviral activity against vaccinia virus.

a. Cytotoxicity Assay

Cytopathic effect was measured on the BSC40 african green monkey kidney cells using 100 μM concentrations of the compounds tested in silico. In this assay, 96-well black Packard viewplates were seeded with BSC40 cells ($2.25x10^4$ cells/well) in Minimum Essential Media supplemented with 5% FCS, 2mM L-glutamine and 10 μg/mL gentamycin sulfate. When the cells became confluent (24 hrs) they were treated with 100 μM compound diluted in media. The cells were placed in an incubator at 37°C (5% CO_2) for 24 hours, and checked for toxicity via direct observation under the microscope and also with alamar blue which assesses cell viability and proliferation (healthy cells produce a visible color change from blue to red). The cells were scored on a scale of 0-3 where 0 corresponds to normal healthy cells, 1 corresponds to unhealthy cells but not rounding up, 2 corresponds to cells that are rounding up, and 3 corresponds to cells that have rounded up and pulled off the plate. Compounds at concentrations that scored 1 or greater were diluted and the above assay was repeated to find the concentration at which the compound scored 0.

It was found that TTP-A exhibited a TC50 value of about 900 μM, and TTP-B exhibited a TC50 value of about 600 μM.

b. Anti-viral assay

A vvGFP assay may be performed to test the ability of each compound to inhibit viral growth as measured by a reduction in fluorescence from vaccinia virus

expressing the green fluorescent protein (vvGFP). In this assay, 96-well black Packard viewplates are seeded with BSC40 cells in Minimum Essential Media supplemented with 5% FCS, 2mM L-glutamine, and 10 μg/mL gentamycin sulfate. When the cells are confluent they are washed with PBS and then infected with vaccinia virus at a multiplicity of infection (MOI) of 0.1 for 30 min in PBS. At 30 minutes, the cells are overlaid with 100 μl of infection media supplemented with the compound of interest in doubling dilutions. As controls, infected cells are treated with rifampicin (to block assembly of DNA and protein into mature virus particles), AraC, hydroxyurea, with no compound, or mock infected. Cells are put in a 37°C incubator (5% CO_2) for 24 hrs. At 24 hours post infection (pi), the plates are removed from the incubator, washed with PBS and fluorescence measured on a Wallac plate reader (using an excitation of 485 nm and reading at 535 nm). Wells that show reduced fluorescence are checked visually under the microscope to verify a reduction in viral infection versus a loss of cells due to cytopathic effect from virus infection. Compounds that are found to inhibit viral replication are then checked for inhibitory effect at various concentrations to determine the IC_{50} and the therapeutic index. It was found that TTP-A exhibited a IC50 value of about 12 μM, and TTP-B exhibited a IC50 value of about 4.6 μM.

c. Determination of TI

The 50% inhibitor concentrations (IC50) were determined by cytopathic effect (CPE) inhibition as seen by fluorescence using vvGFP and plaque reduction assays with crystal violet staining or neutral red uptake. The 50% cell toxicity concentration (TC50) were determined as the concentrations of compounds that caused 50% of the cells to round up and show signs of toxicity both visibly and by the Alamar Blue dye assay. The therapeutic index was calculated as the value for TC50 divided by IC50. For TTP-A, a TI of about 75 was calculated. For TTP-B, a TI of about 130 was calculated.

Example 3: Drug-Resistant Viruses

To demonstrate that the target of TTP-A mediated inhibition is I7L protein, vvGFP was subjected to numerous passages in the presence of TTP-A to generate durg-resistant viral mutants (Byrd, C.M., et al., 2004, *J. Virol.* **78**:12147-12156). Cells were infected with vvGFP at an MOI of 0.1 in the presence of the IC50 concentration of TTP-A for 24 h prior to being harvested. After determinining the

titer, a portion of the virus-infected cell extract was used to infect fresh BSC40 cells. The titer of virus dropped seven logs from passage 0 to 4. Starting with passage 5, the progeny titer began to rise in the presence of the drug until a four log increase was observed by passage 7, presumably due to the emergence of a drug-resistant mutant population. After passage 9, individual viral plaques were purified, and the viral DNA isolated and sequenced. All of the resistant viruses were found to have mutations in positions 104 and 324, with a Y to C mutation at 104, and an L to M mutation at 324. FIG. 5 shows a model of the I7L active site showing the position of Leu324 in close proximity to the catalytic cysteine, Cys328.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth herein may be applicable as a consequence of variations in the responsiveness of the mammal being treated for orthopox-mediated disease(s). Likewise, the specific pharmacological responses observed may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention.

TABLE -2

REMARK Model of I7L cysteine protease domain
REMARK

ATOM	1	N	LYS	120	35.399	18.046	91.616	1.00 33.54
ATOM	2	CA	LYS	120	36.155	19.054	90.839	1.00 33.54
ATOM	3	CB	LYS	120	36.788	18.386	89.607	1.00 33.54
ATOM	4	CG	LYS	120	37.840	17.338	89.979	1.00 33.54
ATOM	5	CD	LYS	120	38.181	16.372	88.842	1.00 33.54
ATOM	6	CE	LYS	120	39.240	15.329	89.215	1.00 33.54
ATOM	7	NZ	LYS	120	39.370	14.324	88.133	1.00 33.54
ATOM	8	C	LYS	120	35.214	20.123	90.391	1.00 33.54
ATOM	9	O	LYS	120	34.007	19.904	90.314	1.00 33.54
ATOM	10	N	PRO	121	35.732	21.292	90.132	1.00130.82
ATOM	11	CA	PRO	121	34.868	22.345	89.684	1.00130.82
ATOM	12	CD	PRO	121	36.861	21.796	90.893	1.00130.82
ATOM	13	CB	PRO	121	35.646	23.643	89.883	1.00130.82
ATOM	14	CG	PRO	121	36.621	23.308	91.027	1.00130.82
ATOM	15	C	PRO	121	34.458	22.088	88.276	1.00130.82
ATOM	16	O	PRO	121	35.303	21.715	87.465	1.00130.82
ATOM	17	N	ARG	122	33.164	22.271	87.970	1.00108.62
ATOM	18	CA	ARG	122	32.676	22.105	86.635	1.00108.62
ATOM	19	CB	ARG	122	31.139	22.137	86.561	1.00108.62
ATOM	20	CG	ARG	122	30.463	21.010	87.349	1.00108.62
ATOM	21	CD	ARG	122	30.257	19.714	86.559	1.00108.62
ATOM	22	NE	ARG	122	31.599	19.128	86.270	1.00108.62
ATOM	23	CZ	ARG	122	32.195	19.334	85.057	1.00108.62
ATOM	24	NH1	ARG	122	31.553	20.056	84.094	1.00108.62
ATOM	25	NH2	ARG	122	33.429	18.808	84.806	1.00108.62
ATOM	26	C	ARG	122	33.186	23.250	85.820	1.00108.62
ATOM	27	O	ARG	122	33.508	23.103	84.643	1.00108.62
ATOM	28	N	LEU	123	33.260	24.433	86.458	1.00 72.61
ATOM	29	CA	LEU	123	33.634	25.666	85.824	1.00 72.61
ATOM	30	CB	LEU	123	33.074	26.863	86.591	1.00 72.61
ATOM	31	CG	LEU	123	33.617	28.215	86.135	1.00 72.61
ATOM	32	CD2	LEU	123	33.353	29.259	87.223	1.00 72.61
ATOM	33	CD1	LEU	123	33.125	28.598	84.735	1.00 72.61
ATOM	34	C	LEU	123	35.117	25.813	85.846	1.00 72.61
ATOM	35	O	LEU	123	35.709	26.039	86.898	1.00 72.61
ATOM	36	N	ARG	124	35.742	25.733	84.657	1.00 69.73
ATOM	37	CA	ARG	124	37.165	25.842	84.529	1.00 69.73
ATOM	38	CB	ARG	124	37.696	25.293	83.192	1.00 69.73
ATOM	39	CG	ARG	124	37.332	23.830	82.919	1.00 69.73
ATOM	40	CD	ARG	124	37.850	23.313	81.573	1.00 69.73
ATOM	41	NE	ARG	124	37.270	21.957	81.360	1.00 69.73
ATOM	42	CZ	ARG	124	37.185	21.439	80.100	1.00 69.73
ATOM	43	NH1	ARG	124	37.678	22.141	79.037	1.00 69.73
ATOM	44	NH2	ARG	124	36.598	20.222	79.901	1.00 69.73
ATOM	45	C	ARG	124	37.513	27.293	84.548	1.00 69.73
ATOM	46	O	ARG	124	36.703	28.143	84.182	1.00 69.73
ATOM	47	N	GLU	125	38.736	27.625	85.002	1.00 99.91
ATOM	48	CA	GLU	125	39.122	28.999	84.932	1.00 99.91
ATOM	49	CB	GLU	125	39.774	29.571	86.198	1.00 99.91
ATOM	50	CG	GLU	125	41.124	28.962	86.547	1.00 99.91
ATOM	51	CD	GLU	125	41.597	29.709	87.780	1.00 99.91
ATOM	52	OE1	GLU	125	41.288	30.928	87.873	1.00 99.91
ATOM	53	OE2	GLU	125	42.257	29.078	88.646	1.00 99.91
ATOM	54	C	GLU	125	40.099	29.093	83.812	1.00 99.91
ATOM	55	O	GLU	125	40.881	28.175	83.570	1.00 99.91
ATOM	56	N	LYS	126	40.057	30.220	83.085	1.00124.58
ATOM	57	CA	LYS	126	40.858	30.377	81.910	1.00124.58
ATOM	58	CB	LYS	126	40.290	31.417	80.932	1.00124.58
ATOM	59	CG	LYS	126	38.982	30.960	80.284	1.00124.58
ATOM	60	CD	LYS	126	37.862	30.713	81.296	1.00124.58
ATOM	61	CE	LYS	126	37.580	31.908	82.209	1.00124.58

ATOM	62	NZ	LYS	126	36.552	31.544	83.207	1.00	124.58
ATOM	63	C	LYS	126	42.249	30.784	82.254	1.00	124.58
ATOM	64	O	LYS	126	42.528	31.325	83.322	1.00	124.58
ATOM	65	N	VAL	127	43.162	30.486	81.309	1.00	43.57
ATOM	66	CA	VAL	127	44.543	30.843	81.385	1.00	43.57
ATOM	67	CB	VAL	127	45.391	30.078	80.411	1.00	43.57
ATOM	68	CG1	VAL	127	46.853	30.528	80.553	1.00	43.57
ATOM	69	CG2	VAL	127	45.177	28.575	80.660	1.00	43.57
ATOM	70	C	VAL	127	44.590	32.296	81.023	1.00	43.57
ATOM	71	O	VAL	127	43.634	32.836	80.472	1.00	43.57
ATOM	72	N	SER	128	45.701	32.975	81.361	1.00	27.55
ATOM	73	CA	SER	128	45.817	34.385	81.130	1.00	27.55
ATOM	74	CB	SER	128	47.193	34.936	81.534	1.00	27.55
ATOM	75	OG	SER	128	47.397	34.783	82.931	1.00	27.55
ATOM	76	C	SER	128	45.641	34.676	79.673	1.00	27.55
ATOM	77	O	SER	128	44.968	35.638	79.309	1.00	27.55
ATOM	78	N	LYS	129	46.229	33.845	78.792	1.00	93.74
ATOM	79	CA	LYS	129	46.155	34.125	77.387	1.00	93.74
ATOM	80	CB	LYS	129	46.873	33.071	76.522	1.00	93.74
ATOM	81	CG	LYS	129	46.278	31.664	76.647	1.00	93.74
ATOM	82	CD	LYS	129	46.694	30.709	75.522	1.00	93.74
ATOM	83	CE	LYS	129	46.082	29.310	75.632	1.00	93.74
ATOM	84	NZ	LYS	129	46.523	28.653	76.883	1.00	93.74
ATOM	85	C	LYS	129	44.722	34.126	76.961	1.00	93.74
ATOM	86	O	LYS	129	44.268	35.036	76.268	1.00	93.74
ATOM	87	N	ALA	130	43.965	33.103	77.394	1.00	27.03
ATOM	88	CA	ALA	130	42.599	32.952	76.991	1.00	27.03
ATOM	89	CB	ALA	130	41.962	31.668	77.545	1.00	27.03
ATOM	90	C	ALA	130	41.786	34.106	77.481	1.00	27.03
ATOM	91	O	ALA	130	40.931	34.618	76.760	1.00	27.03
ATOM	92	N	ILE	131	42.031	34.550	78.728	1.00	34.84
ATOM	93	CA	ILE	131	41.253	35.613	79.303	1.00	34.84
ATOM	94	CB	ILE	131	41.617	35.916	80.726	1.00	34.84
ATOM	95	CG2	ILE	131	40.905	37.219	81.125	1.00	34.84
ATOM	96	CG1	ILE	131	41.279	34.722	81.635	1.00	34.84
ATOM	97	CD1	ILE	131	41.796	34.881	83.065	1.00	34.84
ATOM	98	C	ILE	131	41.446	36.870	78.517	1.00	34.84
ATOM	99	O	ILE	131	40.492	37.605	78.266	1.00	34.84
ATOM	100	N	ASP	132	42.691	37.148	78.100	1.00	68.91
ATOM	101	CA	ASP	132	42.986	38.364	77.403	1.00	68.91
ATOM	102	CB	ASP	132	44.470	38.463	77.009	1.00	68.91
ATOM	103	CG	ASP	132	44.720	39.870	76.490	1.00	68.91
ATOM	104	OD1	ASP	132	43.756	40.683	76.514	1.00	68.91
ATOM	105	OD2	ASP	132	45.872	40.152	76.063	1.00	68.91
ATOM	106	C	ASP	132	42.186	38.398	76.141	1.00	68.91
ATOM	107	O	ASP	132	41.673	39.443	75.746	1.00	68.91
ATOM	108	N	PHE	133	42.048	37.232	75.485	1.00	73.74
ATOM	109	CA	PHE	133	41.365	37.133	74.230	1.00	73.74
ATOM	110	CB	PHE	133	41.384	35.691	73.696	1.00	73.74
ATOM	111	CG	PHE	133	40.936	35.690	72.275	1.00	73.74
ATOM	112	CD1	PHE	133	41.817	36.027	71.274	1.00	73.74
ATOM	113	CD2	PHE	133	39.649	35.344	71.943	1.00	73.74
ATOM	114	CE1	PHE	133	41.416	36.025	69.958	1.00	73.74
ATOM	115	CE2	PHE	133	39.242	35.341	70.629	1.00	73.74
ATOM	116	CZ	PHE	133	40.126	35.683	69.635	1.00	73.74
ATOM	117	C	PHE	133	39.943	37.555	74.434	1.00	73.74
ATOM	118	O	PHE	133	39.386	38.308	73.634	1.00	73.74
ATOM	119	N	SER	134	39.316	37.087	75.529	1.00	70.77
ATOM	120	CA	SER	134	37.947	37.423	75.794	1.00	70.77
ATOM	121	CB	SER	134	37.418	36.775	77.085	1.00	70.77
ATOM	122	OG	SER	134	37.409	35.360	76.959	1.00	70.77
ATOM	123	C	SER	134	37.831	38.909	75.958	1.00	70.77
ATOM	124	O	SER	134	36.913	39.529	75.424	1.00	70.77
ATOM	125	N	GLN	135	38.783	39.529	76.677	1.00	36.15
ATOM	126	CA	GLN	135	38.709	40.937	76.956	1.00	36.15
ATOM	127	CB	GLN	135	39.893	41.434	77.808	1.00	36.15

ATOM	128	CG	GLN	135	39.866	42.932	78.126	1.00 36.15
ATOM	129	CD	GLN	135	38.813	43.192	79.191	1.00 36.15
ATOM	130	OE1	GLN	135	37.713	42.647	79.137	1.00 36.15
ATOM	131	NE2	GLN	135	39.162	44.045	80.192	1.00 36.15
ATOM	132	C	GLN	135	38.731	41.714	75.675	1.00 36.15
ATOM	133	O	GLN	135	37.973	42.668	75.510	1.00 36.15
ATOM	134	N	MET	136	39.596	41.316	74.724	1.00 31.95
ATOM	135	CA	MET	136	39.739	42.050	73.500	1.00 31.95
ATOM	136	CB	MET	136	40.810	41.436	72.586	1.00 31.95
ATOM	137	CG	MET	136	42.207	41.448	73.209	1.00 31.95
ATOM	138	SD	MET	136	43.465	40.522	72.280	1.00 31.95
ATOM	139	CE	MET	136	43.593	41.727	70.929	1.00 31.95
ATOM	140	C	MET	136	38.447	42.026	72.743	1.00 31.95
ATOM	141	O	MET	136	38.001	43.051	72.228	1.00 31.95
ATOM	142	N	ASP	137	37.800	40.849	72.676	1.00 41.81
ATOM	143	CA	ASP	137	36.595	40.710	71.914	1.00 41.81
ATOM	144	CB	ASP	137	36.073	39.264	71.857	1.00 41.81
ATOM	145	CG	ASP	137	36.953	38.498	70.877	1.00 41.81
ATOM	146	OD1	ASP	137	37.243	39.059	69.786	1.00 41.81
ATOM	147	OD2	ASP	137	37.336	37.341	71.198	1.00 41.81
ATOM	148	C	ASP	137	35.519	41.570	72.501	1.00 41.81
ATOM	149	O	ASP	137	34.735	42.177	71.776	1.00 41.81
ATOM	150	N	LEU	138	35.467	41.658	73.838	1.00100.75
ATOM	151	CA	LEU	138	34.440	42.407	74.494	1.00100.75
ATOM	152	CB	LEU	138	34.625	42.351	76.028	1.00100.75
ATOM	153	CG	LEU	138	33.547	43.003	76.929	1.00100.75
ATOM	154	CD2	LEU	138	33.267	44.480	76.598	1.00100.75
ATOM	155	CD1	LEU	138	33.931	42.830	78.409	1.00100.75
ATOM	156	C	LEU	138	34.552	43.836	74.043	1.00100.75
ATOM	157	O	LEU	138	33.543	44.490	73.785	1.00100.75
ATOM	158	N	LYS	139	35.786	44.362	73.951	1.00110.99
ATOM	159	CA	LYS	139	36.007	45.744	73.630	1.00110.99
ATOM	160	CB	LYS	139	37.415	46.265	73.985	1.00110.99
ATOM	161	CG	LYS	139	38.580	45.713	73.166	1.00110.99
ATOM	162	CD	LYS	139	39.861	46.515	73.415	1.00110.99
ATOM	163	CE	LYS	139	41.113	45.959	72.734	1.00110.99
ATOM	164	NZ	LYS	139	42.277	46.819	73.056	1.00110.99
ATOM	165	C	LYS	139	35.696	46.112	72.205	1.00110.99
ATOM	166	O	LYS	139	35.380	47.274	71.954	1.00110.99
ATOM	167	N	ILE	140	35.784	45.154	71.252	1.00182.56
ATOM	168	CA	ILE	140	35.662	45.367	69.825	1.00182.56
ATOM	169	CB	ILE	140	35.394	44.076	69.090	1.00182.56
ATOM	170	CG2	ILE	140	33.944	43.652	69.362	1.00182.56
ATOM	171	CG1	ILE	140	35.744	44.188	67.600	1.00182.56
ATOM	172	CD1	ILE	140	34.883	45.179	66.830	1.00182.56
ATOM	173	C	ILE	140	34.591	46.380	69.511	1.00182.56
ATOM	174	O	ILE	140	33.449	46.280	69.954	1.00182.56
ATOM	175	N	ASP	141	34.971	47.425	68.741	1.00152.17
ATOM	176	CA	ASP	141	34.097	48.531	68.453	1.00152.17
ATOM	177	CB	ASP	141	34.810	49.688	67.725	1.00152.17
ATOM	178	CG	ASP	141	33.873	50.896	67.721	1.00152.17
ATOM	179	OD1	ASP	141	32.825	50.827	68.417	1.00152.17
ATOM	180	OD2	ASP	141	34.188	51.898	67.025	1.00152.17
ATOM	181	C	ASP	141	32.925	48.138	67.605	1.00152.17
ATOM	182	O	ASP	141	31.792	48.505	67.908	1.00152.17
ATOM	183	N	ASP	142	33.155	47.380	66.517	1.00218.47
ATOM	184	CA	ASP	142	32.078	47.107	65.608	1.00218.47
ATOM	185	CB	ASP	142	32.531	47.058	64.141	1.00218.47
ATOM	186	CG	ASP	142	31.310	47.289	63.266	1.00218.47
ATOM	187	OD1	ASP	142	30.632	48.335	63.458	1.00218.47
ATOM	188	OD2	ASP	142	31.049	46.429	62.382	1.00218.47
ATOM	189	C	ASP	142	31.409	45.813	65.949	1.00218.47
ATOM	190	O	ASP	142	31.944	44.984	66.683	1.00218.47
ATOM	191	N	LEU	143	30.195	45.611	65.401	1.00 82.28
ATOM	192	CA	LEU	143	29.456	44.420	65.681	1.00 82.28
ATOM	193	CB	LEU	143	27.940	44.671	65.688	1.00 82.28

ATOM	194	CG	LEU	143	27.528	45.802	66.656	1.00 82.28
ATOM	195	CD2	LEU	143	28.095	45.575	68.067	1.00 82.28
ATOM	196	CD1	LEU	143	26.009	46.028	66.645	1.00 82.28
ATOM	197	C	LEU	143	29.763	43.467	64.575	1.00 82.28
ATOM	198	O	LEU	143	29.085	43.442	63.548	1.00 82.28
ATOM	199	N	SER	144	30.806	42.642	64.773	1.00 84.93
ATOM	200	CA	SER	144	31.222	41.716	63.764	1.00 84.93
ATOM	201	CB	SER	144	32.744	41.714	63.557	1.00 84.93
ATOM	202	OG	SER	144	33.099	40.782	62.550	1.00 84.93
ATOM	203	C	SER	144	30.811	40.346	64.203	1.00 84.93
ATOM	204	O	SER	144	30.408	40.147	65.349	1.00 84.93
ATOM	205	N	ARG	145	30.893	39.361	63.285	1.00 99.45
ATOM	206	CA	ARG	145	30.495	38.020	63.611	1.00 99.45
ATOM	207	CB	ARG	145	29.996	37.210	62.402	1.00 99.45
ATOM	208	CG	ARG	145	31.049	37.044	61.307	1.00 99.45
ATOM	209	CD	ARG	145	30.544	36.270	60.089	1.00 99.45
ATOM	210	NE	ARG	145	31.664	36.206	59.108	1.00 99.45
ATOM	211	CZ	ARG	145	31.393	36.165	57.769	1.00 99.45
ATOM	212	NH1	ARG	145	30.102	36.187	57.332	1.00 99.45
ATOM	213	NH2	ARG	145	32.418	36.104	56.870	1.00 99.45
ATOM	214	C	ARG	145	31.681	37.305	64.173	1.00 99.45
ATOM	215	O	ARG	145	32.709	37.159	63.514	1.00 99.45
ATOM	216	N	LYS	146	31.566	36.900	65.454	1.00170.67
ATOM	217	CA	LYS	146	32.599	36.199	66.166	1.00170.67
ATOM	218	CB	LYS	146	32.405	36.207	67.689	1.00170.67
ATOM	219	CG	LYS	146	33.548	35.509	68.432	1.00170.67
ATOM	220	CD	LYS	146	34.895	36.235	68.340	1.00170.67
ATOM	221	CE	LYS	146	35.822	35.707	67.238	1.00170.67
ATOM	222	NZ	LYS	146	35.493	36.331	65.938	1.00170.67
ATOM	223	C	LYS	146	32.714	34.770	65.741	1.00170.67
ATOM	224	O	LYS	146	33.812	34.216	65.711	1.00170.67
ATOM	225	N	GLY	147	31.578	34.107	65.446	1.00 42.81
ATOM	226	CA	GLY	147	31.717	32.728	65.079	1.00 42.81
ATOM	227	C	GLY	147	30.442	32.253	64.477	1.00 42.81
ATOM	228	O	GLY	147	29.360	32.720	64.831	1.00 42.81
ATOM	229	N	ILE	148	30.559	31.317	63.517	1.00135.88
ATOM	230	CA	ILE	148	29.411	30.705	62.922	1.00135.88
ATOM	231	CB	ILE	148	29.117	31.213	61.533	1.00135.88
ATOM	232	CG2	ILE	148	30.364	31.015	60.657	1.00135.88
ATOM	233	CG1	ILE	148	27.850	30.548	60.974	1.00135.88
ATOM	234	CD1	ILE	148	26.568	30.951	61.702	1.00135.88
ATOM	235	C	ILE	148	29.693	29.237	62.839	1.00135.88
ATOM	236	O	ILE	148	30.700	28.824	62.265	1.00135.88
ATOM	237	N	HIS	149	28.822	28.397	63.435	1.00129.16
ATOM	238	CA	HIS	149	29.042	26.989	63.306	1.00129.16
ATOM	239	ND1	HIS	149	31.259	24.787	62.306	1.00129.16
ATOM	240	CG	HIS	149	30.723	25.107	63.534	1.00129.16
ATOM	241	CB	HIS	149	30.353	26.501	63.947	1.00129.16
ATOM	242	NE2	HIS	149	31.102	22.884	63.445	1.00129.16
ATOM	243	CD2	HIS	149	30.633	23.933	64.217	1.00129.16
ATOM	244	CE1	HIS	149	31.468	23.446	62.307	1.00129.16
ATOM	245	C	HIS	149	27.912	26.272	63.973	1.00129.16
ATOM	246	O	HIS	149	27.326	26.763	64.935	1.00129.16
ATOM	247	N	THR	150	27.571	25.081	63.445	1.00179.98
ATOM	248	CA	THR	150	26.541	24.248	63.993	1.00179.98
ATOM	249	CB	THR	150	26.887	23.769	65.380	1.00179.98
ATOM	250	OG1	THR	150	28.162	23.143	65.354	1.00179.98
ATOM	251	CG2	THR	150	25.847	22.736	65.856	1.00179.98
ATOM	252	C	THR	150	25.249	25.014	64.002	1.00179.98
ATOM	253	O	THR	150	24.363	24.774	64.819	1.00179.98
ATOM	254	N	GLY	151	25.097	25.967	63.066	1.00 40.25
ATOM	255	CA	GLY	151	23.842	26.653	62.928	1.00 40.25
ATOM	256	C	GLY	151	23.686	27.753	63.937	1.00 40.25
ATOM	257	O	GLY	151	22.580	28.261	64.119	1.00 40.25
ATOM	258	N	GLU	152	24.761	28.150	64.641	1.00 77.36
ATOM	259	CA	GLU	152	24.597	29.251	65.551	1.00 77.36

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ATOM    260  CB  GLU   152      24.867  28.897  67.024  1.00 77.36
ATOM    261  CG  GLU   152      24.688  30.087  67.968  1.00 77.36
ATOM    262  CD  GLU   152      23.221  30.490  67.936  1.00 77.36
ATOM    263  OE1 GLU   152      22.411  29.729  67.341  1.00 77.36
ATOM    264  OE2 GLU   152      22.889  31.567  68.502  1.00 77.36
ATOM    265  C   GLU   152      25.591  30.299  65.157  1.00 77.36
ATOM    266  O   GLU   152      26.781  30.013  65.031  1.00 77.36
ATOM    267  N   ASN   153      25.124  31.550  64.945  1.00 91.83
ATOM    268  CA  ASN   153      26.033  32.588  64.543  1.00 91.83
ATOM    269  CB  ASN   153      25.602  33.279  63.233  1.00 91.83
ATOM    270  CG  ASN   153      26.803  33.990  62.619  1.00 91.83
ATOM    271  OD1 ASN   153      27.948  33.754  62.997  1.00 91.83
ATOM    272  ND2 ASN   153      26.539  34.882  61.626  1.00 91.83
ATOM    273  C   ASN   153      26.041  33.642  65.611  1.00 91.83
ATOM    274  O   ASN   153      25.048  34.346  65.798  1.00 91.83
ATOM    275  N   PRO   154      27.105  33.707  66.372  1.00157.76
ATOM    276  CA  PRO   154      27.188  34.780  67.333  1.00157.76
ATOM    277  CD  PRO   154      27.523  32.448  66.972  1.00157.76
ATOM    278  CB  PRO   154      27.889  34.220  68.566  1.00157.76
ATOM    279  CG  PRO   154      27.607  32.717  68.482  1.00157.76
ATOM    280  C   PRO   154      27.835  36.021  66.801  1.00157.76
ATOM    281  O   PRO   154      28.727  35.922  65.960  1.00157.76
ATOM    282  N   LYS   155      27.438  37.199  67.318  1.00104.45
ATOM    283  CA  LYS   155      28.029  38.426  66.881  1.00104.45
ATOM    284  CB  LYS   155      27.046  39.365  66.161  1.00104.45
ATOM    285  CG  LYS   155      27.707  40.594  65.537  1.00104.45
ATOM    286  CD  LYS   155      26.855  41.257  64.452  1.00104.45
ATOM    287  CE  LYS   155      26.808  40.455  63.149  1.00104.45
ATOM    288  NZ  LYS   155      25.975  41.155  62.145  1.00104.45
ATOM    289  C   LYS   155      28.544  39.103  68.106  1.00104.45
ATOM    290  O   LYS   155      28.388  38.600  69.218  1.00104.45
ATOM    291  N   VAL   156      29.200  40.260  67.927  1.00 41.94
ATOM    292  CA  VAL   156      29.761  40.976  69.035  1.00 41.94
ATOM    293  CB  VAL   156      30.480  42.221  68.612  1.00 41.94
ATOM    294  CG1 VAL   156      30.916  42.988  69.872  1.00 41.94
ATOM    295  CG2 VAL   156      31.643  41.816  67.688  1.00 41.94
ATOM    296  C   VAL   156      28.653  41.373  69.958  1.00 41.94
ATOM    297  O   VAL   156      28.822  41.350  71.176  1.00 41.94
ATOM    298  N   VAL   157      27.485  41.744  69.400  1.00 88.03
ATOM    299  CA  VAL   157      26.391  42.181  70.216  1.00 88.03
ATOM    300  CB  VAL   157      25.167  42.545  69.417  1.00 88.03
ATOM    301  CG1 VAL   157      25.470  43.799  68.581  1.00 88.03
ATOM    302  CG2 VAL   157      24.767  41.331  68.561  1.00 88.03
ATOM    303  C   VAL   157      26.013  41.083  71.161  1.00 88.03
ATOM    304  O   VAL   157      25.806  41.332  72.348  1.00 88.03
ATOM    305  N   LYS   158      25.917  39.834  70.665  1.00119.29
ATOM    306  CA  LYS   158      25.521  38.739  71.508  1.00119.29
ATOM    307  CB  LYS   158      25.321  37.413  70.741  1.00119.29
ATOM    308  CG  LYS   158      26.593  36.599  70.458  1.00119.29
ATOM    309  CD  LYS   158      27.086  35.767  71.651  1.00119.29
ATOM    310  CE  LYS   158      28.435  35.080  71.430  1.00119.29
ATOM    311  NZ  LYS   158      28.872  34.421  72.683  1.00119.29
ATOM    312  C   LYS   158      26.581  38.514  72.542  1.00119.29
ATOM    313  O   LYS   158      26.291  38.253  73.708  1.00119.29
ATOM    314  N   MET   159      27.851  38.634  72.120  1.00113.21
ATOM    315  CA  MET   159      29.002  38.350  72.933  1.00113.21
ATOM    316  CB  MET   159      30.299  38.614  72.151  1.00113.21
ATOM    317  CG  MET   159      31.591  38.338  72.916  1.00113.21
ATOM    318  SD  MET   159      31.999  36.577  73.119  1.00113.21
ATOM    319  CE  MET   159      33.744  36.913  73.488  1.00113.21
ATOM    320  C   MET   159      29.017  39.259  74.127  1.00113.21
ATOM    321  O   MET   159      29.371  38.840  75.228  1.00113.21
ATOM    322  N   LYS   160      28.612  40.527  73.928  1.00132.62
ATOM    323  CA  LYS   160      28.633  41.576  74.914  1.00132.62
ATOM    324  CB  LYS   160      28.228  42.940  74.336  1.00132.62
ATOM    325  CG  LYS   160      28.501  44.097  75.296  1.00132.62
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ATOM    326  CD  LYS   160      28.568  45.457  74.602  1.00132.62
ATOM    327  CE  LYS   160      29.870  45.660  73.822  1.00132.62
ATOM    328  NZ  LYS   160      29.891  47.006  73.208  1.00132.62
ATOM    329  C   LYS   160      27.727  41.236  76.058  1.00132.62
ATOM    330  O   LYS   160      27.816  41.824  77.136  1.00132.62
ATOM    331  N   ILE   161      26.778  40.318  75.834  1.00105.62
ATOM    332  CA  ILE   161      25.916  39.853  76.882  1.00105.62
ATOM    333  CB  ILE   161      24.969  38.804  76.397  1.00105.62
ATOM    334  CG2 ILE   161      24.558  37.977  77.615  1.00105.62
ATOM    335  CG1 ILE   161      23.824  39.418  75.571  1.00105.62
ATOM    336  CD1 ILE   161      24.275  40.036  74.249  1.00105.62
ATOM    337  C   ILE   161      26.761  39.222  77.955  1.00105.62
ATOM    338  O   ILE   161      26.429  39.283  79.139  1.00105.62
ATOM    339  N   GLU   162      27.855  38.558  77.539  1.00101.65
ATOM    340  CA  GLU   162      28.791  37.835  78.359  1.00101.65
ATOM    341  CB  GLU   162      29.857  37.115  77.510  1.00101.65
ATOM    342  CG  GLU   162      29.289  36.055  76.558  1.00101.65
ATOM    343  CD  GLU   162      29.022  34.784  77.353  1.00101.65
ATOM    344  OE1 GLU   162      29.807  34.514  78.300  1.00101.65
ATOM    345  OE2 GLU   162      28.039  34.066  77.023  1.00101.65
ATOM    346  C   GLU   162      29.520  38.760  79.301  1.00101.65
ATOM    347  O   GLU   162      29.975  38.315  80.349  1.00101.65
ATOM    348  N   PRO   163      29.709  40.011  78.991  1.00149.57
ATOM    349  CA  PRO   163      30.404  40.832  79.941  1.00149.57
ATOM    350  CD  PRO   163      30.143  40.348  77.648  1.00149.57
ATOM    351  CB  PRO   163      30.630  42.156  79.228  1.00149.57
ATOM    352  CG  PRO   163      30.900  41.687  77.784  1.00149.57
ATOM    353  C   PRO   163      29.814  40.854  81.316  1.00149.57
ATOM    354  O   PRO   163      28.611  40.645  81.486  1.00149.57
ATOM    355  N   GLU   164      30.698  41.075  82.303  1.00109.34
ATOM    356  CA  GLU   164      30.451  40.875  83.697  1.00109.34
ATOM    357  CB  GLU   164      31.718  40.952  84.578  1.00109.34
ATOM    358  CG  GLU   164      32.595  39.692  84.553  1.00109.34
ATOM    359  CD  GLU   164      33.467  39.667  83.299  1.00109.34
ATOM    360  OE1 GLU   164      32.901  39.676  82.174  1.00109.34
ATOM    361  OE2 GLU   164      34.716  39.620  83.456  1.00109.34
ATOM    362  C   GLU   164      29.426  41.788  84.262  1.00109.34
ATOM    363  O   GLU   164      28.911  42.701  83.621  1.00109.34
ATOM    364  N   ARG   165      29.114  41.483  85.534  1.00129.57
ATOM    365  CA  ARG   165      28.160  42.146  86.357  1.00129.57
ATOM    366  CB  ARG   165      28.490  43.624  86.611  1.00129.57
ATOM    367  CG  ARG   165      29.804  43.774  87.382  1.00129.57
ATOM    368  CD  ARG   165      29.823  44.959  88.349  1.00129.57
ATOM    369  NE  ARG   165      29.072  44.525  89.562  1.00129.57
ATOM    370  CZ  ARG   165      27.712  44.640  89.597  1.00129.57
ATOM    371  NH1 ARG   165      27.046  45.184  88.536  1.00129.57
ATOM    372  NH2 ARG   165      27.012  44.212  90.687  1.00129.57
ATOM    373  C   ARG   165      26.770  41.983  85.845  1.00129.57
ATOM    374  O   ARG   165      25.997  42.935  85.757  1.00129.57
ATOM    375  N   GLY   166      26.427  40.733  85.489  1.00 25.71
ATOM    376  CA  GLY   166      25.066  40.405  85.201  1.00 25.71
ATOM    377  C   GLY   166      24.588  41.029  83.939  1.00 25.71
ATOM    378  O   GLY   166      23.469  41.537  83.889  1.00 25.71
ATOM    379  N   ALA   167      25.412  41.045  82.881  1.00 39.89
ATOM    380  CA  ALA   167      24.824  41.529  81.673  1.00 39.89
ATOM    381  CB  ALA   167      25.803  41.591  80.487  1.00 39.89
ATOM    382  C   ALA   167      23.765  40.517  81.363  1.00 39.89
ATOM    383  O   ALA   167      23.952  39.327  81.613  1.00 39.89
ATOM    384  N   TRP   168      22.604  40.959  80.841  1.00 48.42
ATOM    385  CA  TRP   168      21.553  40.012  80.588  1.00 48.42
ATOM    386  CB  TRP   168      20.214  40.650  80.184  1.00 48.42
ATOM    387  CG  TRP   168      19.480  41.360  81.299  1.00 48.42
ATOM    388  CD2 TRP   168      18.264  42.095  81.105  1.00 48.42
ATOM    389  CD1 TRP   168      19.780  41.444  82.626  1.00 48.42
ATOM    390  NE1 TRP   168      18.822  42.187  83.277  1.00 48.42
ATOM    391  CE2 TRP   168      17.882  42.594  82.351  1.00 48.42
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ATOM    392  CE3 TRP   168      17.522  42.337  79.985  1.00 48.42
ATOM    393  CZ2 TRP   168      16.750  43.344  82.495  1.00 48.42
ATOM    394  CZ3 TRP   168      16.382  43.094  80.130  1.00 48.42
ATOM    395  CH2 TRP   168      16.003  43.586  81.360  1.00 48.42
ATOM    396  C   TRP   168      21.969  39.125  79.464  1.00 48.42
ATOM    397  O   TRP   168      22.502  39.585  78.456  1.00 48.42
ATOM    398  N   MET   169      21.721  37.810  79.626  1.00113.87
ATOM    399  CA  MET   169      22.065  36.831  78.636  1.00113.87
ATOM    400  CB  MET   169      22.066  35.398  79.189  1.00113.87
ATOM    401  CG  MET   169      22.977  35.218  80.403  1.00113.87
ATOM    402  SD  MET   169      24.741  35.504  80.082  1.00113.87
ATOM    403  CE  MET   169      25.237  35.178  81.797  1.00113.87
ATOM    404  C   MET   169      21.021  36.871  77.569  1.00113.87
ATOM    405  O   MET   169      19.835  37.019  77.859  1.00113.87
ATOM    406  N   SER   170      21.449  36.761  76.295  1.00 44.41
ATOM    407  CA  SER   170      20.522  36.747  75.200  1.00 44.41
ATOM    408  CB  SER   170      21.047  37.460  73.941  1.00 44.41
ATOM    409  OG  SER   170      22.180  36.772  73.432  1.00 44.41
ATOM    410  C   SER   170      20.251  35.320  74.832  1.00 44.41
ATOM    411  O   SER   170      20.873  34.395  75.353  1.00 44.41
ATOM    412  N   ASN   171      19.296  35.114  73.904  1.00104.44
ATOM    413  CA  ASN   171      18.893  33.808  73.463  1.00104.44
ATOM    414  CB  ASN   171      17.732  33.848  72.457  1.00104.44
ATOM    415  CG  ASN   171      18.016  34.953  71.455  1.00104.44
ATOM    416  OD1 ASN   171      19.150  35.139  71.017  1.00104.44
ATOM    417  ND2 ASN   171      16.954  35.717  71.085  1.00104.44
ATOM    418  C   ASN   171      20.036  33.154  72.758  1.00104.44
ATOM    419  O   ASN   171      20.234  31.946  72.869  1.00104.44
ATOM    420  N   ARG   172      20.813  33.945  71.997  1.00 54.25
ATOM    421  CA  ARG   172      21.870  33.392  71.204  1.00 54.25
ATOM    422  CB  ARG   172      22.516  34.441  70.288  1.00 54.25
ATOM    423  CG  ARG   172      21.483  35.000  69.305  1.00 54.25
ATOM    424  CD  ARG   172      22.058  35.740  68.098  1.00 54.25
ATOM    425  NE  ARG   172      20.902  36.112  67.233  1.00 54.25
ATOM    426  CZ  ARG   172      20.306  35.165  66.448  1.00 54.25
ATOM    427  NH1 ARG   172      20.754  33.875  66.474  1.00 54.25
ATOM    428  NH2 ARG   172      19.258  35.503  65.644  1.00 54.25
ATOM    429  C   ARG   172      22.901  32.758  72.085  1.00 54.25
ATOM    430  O   ARG   172      23.403  31.678  71.777  1.00 54.25
ATOM    431  N   SER   173      23.249  33.407  73.210  1.00 73.33
ATOM    432  CA  SER   173      24.218  32.835  74.104  1.00 73.33
ATOM    433  CB  SER   173      24.556  33.763  75.282  1.00 73.33
ATOM    434  OG  SER   173      25.518  33.149  76.127  1.00 73.33
ATOM    435  C   SER   173      23.647  31.573  74.677  1.00 73.33
ATOM    436  O   SER   173      24.340  30.566  74.810  1.00 73.33
ATOM    437  N   ILE   174      22.348  31.586  75.014  1.00 96.15
ATOM    438  CA  ILE   174      21.744  30.433  75.614  1.00 96.15
ATOM    439  CB  ILE   174      20.293  30.641  75.937  1.00 96.15
ATOM    440  CG2 ILE   174      19.735  29.300  76.446  1.00 96.15
ATOM    441  CG1 ILE   174      20.120  31.803  76.930  1.00 96.15
ATOM    442  CD1 ILE   174      20.838  31.583  78.260  1.00 96.15
ATOM    443  C   ILE   174      21.819  29.293  74.642  1.00 96.15
ATOM    444  O   ILE   174      22.172  28.176  75.017  1.00 96.15
ATOM    445  N   LYS   175      21.501  29.548  73.356  1.00 57.53
ATOM    446  CA  LYS   175      21.513  28.498  72.378  1.00 57.53
ATOM    447  CB  LYS   175      21.072  28.944  70.974  1.00 57.53
ATOM    448  CG  LYS   175      21.119  27.794  69.964  1.00 57.53
ATOM    449  CD  LYS   175      21.869  26.552  70.448  1.00 57.53
ATOM    450  CE  LYS   175      23.357  26.545  70.092  1.00 57.53
ATOM    451  NZ  LYS   175      23.651  25.411  69.188  1.00 57.53
ATOM    452  C   LYS   175      22.897  27.961  72.228  1.00 57.53
ATOM    453  O   LYS   175      23.090  26.751  72.121  1.00 57.53
ATOM    454  N   ASN   176      23.906  28.846  72.220  1.00 42.26
ATOM    455  CA  ASN   176      25.247  28.390  71.997  1.00 42.26
ATOM    456  CB  ASN   176      26.279  29.530  72.010  1.00 42.26
ATOM    457  CG  ASN   176      27.581  28.964  71.463  1.00 42.26
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ATOM    458  OD1 ASN   176      27.661  27.787  71.116  1.00 42.26
ATOM    459  ND2 ASN   176      28.637  29.819  71.389  1.00 42.26
ATOM    460  C   ASN   176      25.631  27.426  73.082  1.00 42.26
ATOM    461  O   ASN   176      26.225  26.382  72.812  1.00 42.26
ATOM    462  N   LEU   177      25.284  27.734  74.347  1.00 56.01
ATOM    463  CA  LEU   177      25.700  26.878  75.425  1.00 56.01
ATOM    464  CB  LEU   177      25.388  27.413  76.828  1.00 56.01
ATOM    465  CG  LEU   177      25.909  26.443  77.900  1.00 56.01
ATOM    466  CD2 LEU   177      25.411  26.827  79.292  1.00 56.01
ATOM    467  CD1 LEU   177      27.438  26.312  77.835  1.00 56.01
ATOM    468  C   LEU   177      25.025  25.556  75.293  1.00 56.01
ATOM    469  O   LEU   177      25.602  24.514  75.597  1.00 56.01
ATOM    470  N   VAL   178      23.765  25.580  74.838  1.00 56.57
ATOM    471  CA  VAL   178      22.968  24.413  74.640  1.00 56.57
ATOM    472  CB  VAL   178      21.687  24.840  73.994  1.00 56.57
ATOM    473  CG1 VAL   178      20.954  23.617  73.470  1.00 56.57
ATOM    474  CG2 VAL   178      20.889  25.678  75.004  1.00 56.57
ATOM    475  C   VAL   178      23.698  23.504  73.693  1.00 56.57
ATOM    476  O   VAL   178      23.829  22.308  73.952  1.00 56.57
ATOM    477  N   SER   179      24.213  24.056  72.576  1.00 79.14
ATOM    478  CA  SER   179      24.884  23.265  71.579  1.00 79.14
ATOM    479  CB  SER   179      25.288  24.075  70.334  1.00 79.14
ATOM    480  OG  SER   179      26.339  24.971  70.655  1.00 79.14
ATOM    481  C   SER   179      26.145  22.690  72.144  1.00 79.14
ATOM    482  O   SER   179      26.496  21.546  71.857  1.00 79.14
ATOM    483  N   GLN   180      26.859  23.474  72.974  1.00128.89
ATOM    484  CA  GLN   180      28.111  23.039  73.526  1.00128.89
ATOM    485  CB  GLN   180      28.745  24.099  74.447  1.00128.89
ATOM    486  CG  GLN   180      29.169  25.386  73.735  1.00128.89
ATOM    487  CD  GLN   180      30.494  25.121  73.032  1.00128.89
ATOM    488  OE1 GLN   180      30.978  23.992  73.010  1.00128.89
ATOM    489  NE2 GLN   180      31.101  26.189  72.447  1.00128.89
ATOM    490  C   GLN   180      27.867  21.823  74.360  1.00128.89
ATOM    491  O   GLN   180      28.607  20.843  74.288  1.00128.89
ATOM    492  N   PHE   181      26.799  21.854  75.174  1.00112.00
ATOM    493  CA  PHE   181      26.451  20.747  76.010  1.00112.00
ATOM    494  CB  PHE   181      25.231  21.043  76.887  1.00112.00
ATOM    495  CG  PHE   181      24.572  19.737  77.130  1.00112.00
ATOM    496  CD1 PHE   181      25.152  18.758  77.896  1.00112.00
ATOM    497  CD2 PHE   181      23.344  19.500  76.566  1.00112.00
ATOM    498  CE1 PHE   181      24.492  17.569  78.089  1.00112.00
ATOM    499  CE2 PHE   181      22.679  18.317  76.763  1.00112.00
ATOM    500  CZ  PHE   181      23.259  17.344  77.532  1.00112.00
ATOM    501  C   PHE   181      26.130  19.562  75.167  1.00112.00
ATOM    502  O   PHE   181      26.570  18.450  75.454  1.00112.00
ATOM    503  N   ALA   182      25.356  19.768  74.092  1.00 29.66
ATOM    504  CA  ALA   182      24.965  18.663  73.275  1.00 29.66
ATOM    505  CB  ALA   182      24.070  19.093  72.100  1.00 29.66
ATOM    506  C   ALA   182      26.192  18.038  72.700  1.00 29.66
ATOM    507  O   ALA   182      26.316  16.815  72.654  1.00 29.66
ATOM    508  N   TYR   183      27.151  18.871  72.267  1.00 86.70
ATOM    509  CA  TYR   183      28.319  18.347  71.629  1.00 86.70
ATOM    510  CB  TYR   183      29.252  19.486  71.164  1.00 86.70
ATOM    511  CG  TYR   183      30.260  18.956  70.203  1.00 86.70
ATOM    512  CD1 TYR   183      29.917  18.769  68.883  1.00 86.70
ATOM    513  CD2 TYR   183      31.546  18.668  70.602  1.00 86.70
ATOM    514  CE1 TYR   183      30.830  18.288  67.975  1.00 86.70
ATOM    515  CE2 TYR   183      32.465  18.186  69.698  1.00 86.70
ATOM    516  CZ  TYR   183      32.109  17.994  68.385  1.00 86.70
ATOM    517  OH  TYR   183      33.050  17.500  67.457  1.00 86.70
ATOM    518  C   TYR   183      29.055  17.492  72.623  1.00 86.70
ATOM    519  O   TYR   183      29.454  16.371  72.316  1.00 86.70
ATOM    520  N   GLY   184      29.246  18.018  73.850  1.00 53.23
ATOM    521  CA  GLY   184      30.008  17.399  74.905  1.00 53.23
ATOM    522  C   GLY   184      29.405  16.176  75.549  1.00 53.23
ATOM    523  O   GLY   184      30.124  15.219  75.821  1.00 53.23
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ATOM	524	N	SER	185	28.088	16.154	75.842	1.00120.41
ATOM	525	CA	SER	185	27.600	15.068	76.658	1.00120.41
ATOM	526	CB	SER	185	26.311	15.371	77.423	1.00120.41
ATOM	527	OG	SER	185	25.920	14.251	78.202	1.00120.41
ATOM	528	C	SER	185	27.382	13.816	75.878	1.00120.41
ATOM	529	O	SER	185	27.009	13.841	74.708	1.00120.41
ATOM	530	N	GLU	186	27.606	12.679	76.574	1.00233.92
ATOM	531	CA	GLU	186	27.606	11.349	76.034	1.00233.92
ATOM	532	CB	GLU	186	28.197	10.300	76.993	1.00233.92
ATOM	533	CG	GLU	186	27.438	10.153	78.313	1.00233.92
ATOM	534	CD	GLU	186	28.204	10.926	79.376	1.00233.92
ATOM	535	OE1	GLU	186	29.463	10.895	79.323	1.00233.92
ATOM	536	OE2	GLU	186	27.549	11.552	80.252	1.00233.92
ATOM	537	C	GLU	186	26.293	10.794	75.573	1.00233.92
ATOM	538	O	GLU	186	26.228	10.305	74.451	1.00233.92
ATOM	539	N	VAL	187	25.197	10.839	76.360	1.00129.80
ATOM	540	CA	VAL	187	24.082	10.104	75.822	1.00129.80
ATOM	541	CB	VAL	187	22.972	9.869	76.789	1.00129.80
ATOM	542	CG1	VAL	187	21.890	9.086	76.036	1.00129.80
ATOM	543	CG2	VAL	187	23.542	9.116	78.006	1.00129.80
ATOM	544	C	VAL	187	23.589	10.872	74.667	1.00129.80
ATOM	545	O	VAL	187	22.963	11.912	74.871	1.00129.80
ATOM	546	N	ASP	188	23.768	10.264	73.471	1.00 52.21
ATOM	547	CA	ASP	188	23.717	10.816	72.144	1.00 52.21
ATOM	548	CB	ASP	188	23.899	9.762	71.036	1.00 52.21
ATOM	549	CG	ASP	188	25.365	9.352	70.982	1.00 52.21
ATOM	550	OD1	ASP	188	26.195	10.032	71.642	1.00 52.21
ATOM	551	OD2	ASP	188	25.672	8.356	70.275	1.00 52.21
ATOM	552	C	ASP	188	22.449	11.526	71.851	1.00 52.21
ATOM	553	O	ASP	188	22.464	12.498	71.095	1.00 52.21
ATOM	554	N	TYR	189	21.319	11.067	72.403	1.00166.36
ATOM	555	CA	TYR	189	20.123	11.786	72.107	1.00166.36
ATOM	556	CB	TYR	189	18.831	11.184	72.665	1.00166.36
ATOM	557	CG	TYR	189	17.733	12.131	72.297	1.00166.36
ATOM	558	CD1	TYR	189	17.390	13.168	73.131	1.00166.36
ATOM	559	CD2	TYR	189	17.057	11.996	71.107	1.00166.36
ATOM	560	CE1	TYR	189	16.385	14.044	72.792	1.00166.36
ATOM	561	CE2	TYR	189	16.051	12.864	70.758	1.00166.36
ATOM	562	CZ	TYR	189	15.714	13.894	71.602	1.00166.36
ATOM	563	OH	TYR	189	14.682	14.789	71.248	1.00166.36
ATOM	564	C	TYR	189	20.307	13.168	72.624	1.00166.36
ATOM	565	O	TYR	189	19.731	14.076	72.027	1.00166.36
ATOM	566	N	ILE	190	21.118	13.292	73.723	1.00202.46
ATOM	567	CA	ILE	190	21.536	14.455	74.472	1.00202.46
ATOM	568	CB	ILE	190	23.029	14.604	74.460	1.00202.46
ATOM	569	CG2	ILE	190	23.560	14.232	73.064	1.00202.46
ATOM	570	CG1	ILE	190	23.425	15.999	74.936	1.00202.46
ATOM	571	CD1	ILE	190	24.932	16.231	74.971	1.00202.46
ATOM	572	C	ILE	190	21.016	15.628	73.777	1.00202.46
ATOM	573	O	ILE	190	21.551	16.067	72.761	1.00202.46
ATOM	574	N	GLY	191	19.934	16.184	74.316	1.00 65.34
ATOM	575	CA	GLY	191	19.400	17.209	73.507	1.00 65.34
ATOM	576	C	GLY	191	19.088	18.352	74.373	1.00 65.34
ATOM	577	O	GLY	191	18.357	18.240	75.355	1.00 65.34
ATOM	578	N	GLN	192	19.694	19.491	74.027	1.00 75.20
ATOM	579	CA	GLN	192	19.282	20.680	74.674	1.00 75.20
ATOM	580	CB	GLN	192	20.381	21.474	75.396	1.00 75.20
ATOM	581	CG	GLN	192	20.750	20.871	76.748	1.00 75.20
ATOM	582	CD	GLN	192	21.729	21.810	77.435	1.00 75.20
ATOM	583	OE1	GLN	192	22.084	22.849	76.882	1.00 75.20
ATOM	584	NE2	GLN	192	22.177	21.440	78.667	1.00 75.20
ATOM	585	C	GLN	192	18.705	21.484	73.573	1.00 75.20
ATOM	586	O	GLN	192	19.316	21.664	72.521	1.00 75.20
ATOM	587	N	PHE	193	17.460	21.929	73.771	1.00131.19
ATOM	588	CA	PHE	193	16.815	22.693	72.758	1.00131.19
ATOM	589	CB	PHE	193	15.278	22.596	72.752	1.00131.19

ATOM	590	CG	PHE	193	14.829	21.254	72.283	1.00131.19
ATOM	591	CD1	PHE	193	14.637	21.019	70.941	1.00131.19
ATOM	592	CD2	PHE	193	14.591	20.238	73.179	1.00131.19
ATOM	593	CE1	PHE	193	14.216	19.787	70.497	1.00131.19
ATOM	594	CE2	PHE	193	14.171	19.004	72.739	1.00131.19
ATOM	595	CZ	PHE	193	13.983	18.777	71.398	1.00131.19
ATOM	596	C	PHE	193	17.109	24.126	73.014	1.00131.19
ATOM	597	O	PHE	193	17.554	24.513	74.095	1.00131.19
ATOM	598	N	ASP	194	16.882	24.941	71.974	1.00136.05
ATOM	599	CA	ASP	194	16.986	26.361	72.067	1.00136.05
ATOM	600	CB	ASP	194	16.874	27.007	70.669	1.00136.05
ATOM	601	CG	ASP	194	16.238	26.078	69.643	1.00136.05
ATOM	602	OD1	ASP	194	15.729	24.995	70.027	1.00136.05
ATOM	603	OD2	ASP	194	16.250	26.455	68.441	1.00136.05
ATOM	604	C	ASP	194	15.780	26.756	72.873	1.00136.05
ATOM	605	O	ASP	194	14.927	25.924	73.178	1.00136.05
ATOM	606	N	MET	195	15.692	28.045	73.242	1.00 86.54
ATOM	607	CA	MET	195	14.641	28.631	74.023	1.00 86.54
ATOM	608	CB	MET	195	14.877	30.130	74.272	1.00 86.54
ATOM	609	CG	MET	195	13.675	30.836	74.900	1.00 86.54
ATOM	610	SD	MET	195	12.979	32.177	73.888	1.00 86.54
ATOM	611	CE	MET	195	11.417	32.271	74.814	1.00 86.54
ATOM	612	C	MET	195	13.348	28.535	73.274	1.00 86.54
ATOM	613	O	MET	195	12.282	28.438	73.881	1.00 86.54
ATOM	614	N	ARG	196	13.415	28.579	71.931	1.00106.06
ATOM	615	CA	ARG	196	12.260	28.602	71.075	1.00106.06
ATOM	616	CB	ARG	196	12.622	28.667	69.581	1.00106.06
ATOM	617	CG	ARG	196	13.170	30.024	69.130	1.00106.06
ATOM	618	CD	ARG	196	12.349	31.207	69.650	1.00106.06
ATOM	619	NE	ARG	196	11.021	31.185	68.972	1.00106.06
ATOM	620	CZ	ARG	196	10.079	32.124	69.285	1.00106.06
ATOM	621	NH1	ARG	196	10.355	33.094	70.209	1.00106.06
ATOM	622	NH2	ARG	196	8.857	32.094	68.677	1.00106.06
ATOM	623	C	ARG	196	11.425	27.371	71.275	1.00106.06
ATOM	624	O	ARG	196	10.203	27.423	71.145	1.00106.06
ATOM	625	N	PHE	197	12.058	26.231	71.600	1.00 81.65
ATOM	626	CA	PHE	197	11.374	24.977	71.747	1.00 81.65
ATOM	627	CB	PHE	197	12.338	23.902	72.276	1.00 81.65
ATOM	628	CG	PHE	197	11.562	22.710	72.718	1.00 81.65
ATOM	629	CD1	PHE	197	11.089	21.800	71.804	1.00 81.65
ATOM	630	CD2	PHE	197	11.325	22.497	74.059	1.00 81.65
ATOM	631	CE1	PHE	197	10.382	20.703	72.225	1.00 81.65
ATOM	632	CE2	PHE	197	10.617	21.397	74.486	1.00 81.65
ATOM	633	CZ	PHE	197	10.144	20.497	73.563	1.00 81.65
ATOM	634	C	PHE	197	10.260	25.112	72.737	1.00 81.65
ATOM	635	O	PHE	197	9.123	24.733	72.453	1.00 81.65
ATOM	636	N	LEU	198	10.546	25.674	73.923	1.00 91.14
ATOM	637	CA	LEU	198	9.522	25.774	74.919	1.00 91.14
ATOM	638	CB	LEU	198	9.988	26.424	76.224	1.00 91.14
ATOM	639	CG	LEU	198	8.832	26.534	77.232	1.00 91.14
ATOM	640	CD2	LEU	198	9.108	27.614	78.284	1.00 91.14
ATOM	641	CD1	LEU	198	8.452	25.160	77.810	1.00 91.14
ATOM	642	C	LEU	198	8.418	26.645	74.418	1.00 91.14
ATOM	643	O	LEU	198	7.243	26.337	74.610	1.00 91.14
ATOM	644	N	ASN	199	8.764	27.760	73.751	1.00 55.60
ATOM	645	CA	ASN	199	7.744	28.685	73.354	1.00 55.60
ATOM	646	CB	ASN	199	8.302	29.888	72.579	1.00 55.60
ATOM	647	CG	ASN	199	9.123	30.720	73.553	1.00 55.60
ATOM	648	OD1	ASN	199	10.349	30.767	73.468	1.00 55.60
ATOM	649	ND2	ASN	199	8.428	31.390	74.511	1.00 55.60
ATOM	650	C	ASN	199	6.765	27.995	72.457	1.00 55.60
ATOM	651	O	ASN	199	5.554	28.097	72.651	1.00 55.60
ATOM	652	N	SER	200	7.264	27.255	71.453	1.00 37.68
ATOM	653	CA	SER	200	6.381	26.626	70.516	1.00 37.68
ATOM	654	CB	SER	200	7.138	25.978	69.348	1.00 37.68
ATOM	655	OG	SER	200	7.729	26.981	68.534	1.00 37.68

ATOM	656	C	SER	200	5.567	25.572	71.203	1.00 37.68
ATOM	657	O	SER	200	4.366	25.448	70.962	1.00 37.68
ATOM	658	N	LEU	201	6.201	24.782	72.087	1.00113.67
ATOM	659	CA	LEU	201	5.505	23.710	72.735	1.00113.67
ATOM	660	CB	LEU	201	6.436	22.946	73.699	1.00113.67
ATOM	661	CG	LEU	201	5.879	21.652	74.334	1.00113.67
ATOM	662	CD2	LEU	201	5.647	20.569	73.270	1.00113.67
ATOM	663	CD1	LEU	201	4.654	21.896	75.231	1.00113.67
ATOM	664	C	LEU	201	4.402	24.300	73.551	1.00113.67
ATOM	665	O	LEU	201	3.253	23.873	73.461	1.00113.67
ATOM	666	N	ALA	202	4.738	25.309	74.375	1.00 48.96
ATOM	667	CA	ALA	202	3.776	25.881	75.269	1.00 48.96
ATOM	668	CB	ALA	202	4.412	26.873	76.260	1.00 48.96
ATOM	669	C	ALA	202	2.685	26.604	74.540	1.00 48.96
ATOM	670	O	ALA	202	1.507	26.362	74.793	1.00 48.96
ATOM	671	N	ILE	203	3.032	27.497	73.591	1.00 52.64
ATOM	672	CA	ILE	203	1.976	28.263	72.987	1.00 52.64
ATOM	673	CB	ILE	203	2.466	29.369	72.100	1.00 52.64
ATOM	674	CG2	ILE	203	1.239	29.999	71.423	1.00 52.64
ATOM	675	CG1	ILE	203	3.299	30.375	72.918	1.00 52.64
ATOM	676	CD1	ILE	203	4.098	31.354	72.060	1.00 52.64
ATOM	677	C	ILE	203	1.109	27.367	72.172	1.00 52.64
ATOM	678	O	ILE	203	-0.112	27.363	72.324	1.00 52.64
ATOM	679	N	HIS	204	1.721	26.555	71.293	1.00151.99
ATOM	680	CA	HIS	204	0.914	25.674	70.508	1.00151.99
ATOM	681	ND1	HIS	204	1.405	27.230	67.048	1.00151.99
ATOM	682	CG	HIS	204	1.285	26.992	68.398	1.00151.99
ATOM	683	CB	HIS	204	1.337	25.630	69.032	1.00151.99
ATOM	684	NE2	HIS	204	1.157	29.214	68.026	1.00151.99
ATOM	685	CD2	HIS	204	1.137	28.211	68.983	1.00151.99
ATOM	686	CE1	HIS	204	1.320	28.578	66.883	1.00151.99
ATOM	687	C	HIS	204	1.139	24.333	71.102	1.00151.99
ATOM	688	O	HIS	204	1.898	23.522	70.574	1.00151.99
ATOM	689	N	GLU	205	0.449	24.066	72.225	1.00156.23
ATOM	690	CA	GLU	205	0.711	22.857	72.933	1.00156.23
ATOM	691	CB	GLU	205	-0.210	22.672	74.150	1.00156.23
ATOM	692	CG	GLU	205	0.028	21.351	74.885	1.00156.23
ATOM	693	CD	GLU	205	-1.067	21.176	75.931	1.00156.23
ATOM	694	OE1	GLU	205	-2.190	20.749	75.548	1.00156.23
ATOM	695	OE2	GLU	205	-0.793	21.465	77.126	1.00156.23
ATOM	696	C	GLU	205	0.462	21.702	72.042	1.00156.23
ATOM	697	O	GLU	205	1.397	20.966	71.737	1.00156.23
ATOM	698	N	LYS	206	-0.782	21.540	71.548	1.00205.50
ATOM	699	CA	LYS	206	-1.007	20.396	70.719	1.00205.50
ATOM	700	CB	LYS	206	-1.205	19.084	71.499	1.00205.50
ATOM	701	CG	LYS	206	-0.059	18.679	72.424	1.00205.50
ATOM	702	CD	LYS	206	-0.356	17.392	73.198	1.00205.50
ATOM	703	CE	LYS	206	-1.759	17.342	73.812	1.00205.50
ATOM	704	NZ	LYS	206	-1.795	18.114	75.073	1.00205.50
ATOM	705	C	LYS	206	-2.308	20.561	70.016	1.00205.50
ATOM	706	O	LYS	206	-3.343	20.732	70.658	1.00205.50
ATOM	707	N	PHE	207	-2.301	20.529	68.671	1.00 72.61
ATOM	708	CA	PHE	207	-3.578	20.476	68.032	1.00 72.61
ATOM	709	CB	PHE	207	-3.496	20.581	66.501	1.00 72.61
ATOM	710	CG	PHE	207	-3.224	22.015	66.198	1.00 72.61
ATOM	711	CD1	PHE	207	-1.956	22.539	66.311	1.00 72.61
ATOM	712	CD2	PHE	207	-4.252	22.837	65.797	1.00 72.61
ATOM	713	CE1	PHE	207	-1.724	23.865	66.030	1.00 72.61
ATOM	714	CE2	PHE	207	-4.025	24.162	65.515	1.00 72.61
ATOM	715	CZ	PHE	207	-2.757	24.679	65.631	1.00 72.61
ATOM	716	C	PHE	207	-4.106	19.138	68.423	1.00 72.61
ATOM	717	O	PHE	207	-5.248	18.997	68.860	1.00 72.61
ATOM	718	N	ASP	208	-3.238	18.118	68.281	1.00124.13
ATOM	719	CA	ASP	208	-3.514	16.787	68.731	1.00124.13
ATOM	720	CB	ASP	208	-3.667	15.769	67.588	1.00124.13
ATOM	721	CG	ASP	208	-5.011	16.013	66.921	1.00124.13

ATOM	722	OD1	ASP	208	-5.724	16.956	67.359	1.00124.13
ATOM	723	OD2	ASP	208	-5.353	15.256	65.974	1.00124.13
ATOM	724	C	ASP	208	-2.297	16.402	69.506	1.00124.13
ATOM	725	O	ASP	208	-2.317	15.487	70.328	1.00124.13
ATOM	726	N	ALA	209	-1.197	17.135	69.250	1.00255.38
ATOM	727	CA	ALA	209	0.058	16.921	69.906	1.00255.38
ATOM	728	CB	ALA	209	0.844	15.720	69.354	1.00255.38
ATOM	729	C	ALA	209	0.860	18.146	69.624	1.00255.38
ATOM	730	O	ALA	209	0.424	18.995	68.849	1.00255.38
ATOM	731	N	PHE	210	2.040	18.286	70.266	1.00276.72
ATOM	732	CA	PHE	210	2.848	19.437	70.008	1.00276.72
ATOM	733	CB	PHE	210	3.978	19.598	71.040	1.00276.72
ATOM	734	CG	PHE	210	4.550	18.246	71.293	1.00276.72
ATOM	735	CD1	PHE	210	5.582	17.725	70.548	1.00276.72
ATOM	736	CD2	PHE	210	4.023	17.486	72.311	1.00276.72
ATOM	737	CE1	PHE	210	6.073	16.471	70.816	1.00276.72
ATOM	738	CE2	PHE	210	4.509	16.234	72.586	1.00276.72
ATOM	739	CZ	PHE	210	5.540	15.722	71.837	1.00276.72
ATOM	740	C	PHE	210	3.365	19.370	68.611	1.00276.72
ATOM	741	O	PHE	210	4.441	18.848	68.335	1.00276.72
ATOM	742	N	MET	211	2.563	19.920	67.681	1.00 90.31
ATOM	743	CA	MET	211	2.873	19.955	66.287	1.00 90.31
ATOM	744	CB	MET	211	1.723	20.500	65.422	1.00 90.31
ATOM	745	CG	MET	211	0.500	19.583	65.367	1.00 90.31
ATOM	746	SD	MET	211	-0.869	20.212	64.350	1.00 90.31
ATOM	747	CE	MET	211	0.015	20.005	62.774	1.00 90.31
ATOM	748	C	MET	211	4.031	20.863	66.088	1.00 90.31
ATOM	749	O	MET	211	4.908	20.603	65.265	1.00 90.31
ATOM	750	N	ASN	212	4.062	21.973	66.845	1.00 90.13
ATOM	751	CA	ASN	212	5.123	22.906	66.637	1.00 90.13
ATOM	752	CB	ASN	212	4.978	24.204	67.447	1.00 90.13
ATOM	753	CG	ASN	212	5.890	25.234	66.791	1.00 90.13
ATOM	754	OD1	ASN	212	7.077	24.987	66.582	1.00 90.13
ATOM	755	ND2	ASN	212	5.326	26.423	66.457	1.00 90.13
ATOM	756	C	ASN	212	6.400	22.233	67.018	1.00 90.13
ATOM	757	O	ASN	212	7.441	22.475	66.413	1.00 90.13
ATOM	758	N	LYS	213	6.345	21.424	68.092	1.00142.77
ATOM	759	CA	LYS	213	7.426	20.654	68.651	1.00142.77
ATOM	760	CB	LYS	213	7.131	20.197	70.088	1.00142.77
ATOM	761	CG	LYS	213	8.178	19.226	70.645	1.00142.77
ATOM	762	CD	LYS	213	8.019	18.934	72.136	1.00142.77
ATOM	763	CE	LYS	213	8.827	17.726	72.617	1.00142.77
ATOM	764	NZ	LYS	213	10.230	17.810	72.158	1.00142.77
ATOM	765	C	LYS	213	7.773	19.407	67.888	1.00142.77
ATOM	766	O	LYS	213	8.928	18.987	67.896	1.00142.77
ATOM	767	N	HIS	214	6.801	18.776	67.202	1.00151.89
ATOM	768	CA	HIS	214	6.993	17.422	66.740	1.00151.89
ATOM	769	ND1	HIS	214	6.475	16.168	63.639	1.00151.89
ATOM	770	CG	HIS	214	5.807	17.013	64.500	1.00151.89
ATOM	771	CB	HIS	214	5.781	16.828	65.991	1.00151.89
ATOM	772	NE2	HIS	214	5.499	17.715	62.378	1.00151.89
ATOM	773	CD2	HIS	214	5.217	17.953	63.712	1.00151.89
ATOM	774	CE1	HIS	214	6.256	16.634	62.383	1.00151.89
ATOM	775	C	HIS	214	8.196	17.269	65.858	1.00151.89
ATOM	776	O	HIS	214	8.878	16.248	65.927	1.00151.89
ATOM	777	N	ILE	215	8.480	18.263	65.001	1.00101.59
ATOM	778	CA	ILE	215	9.542	18.215	64.031	1.00101.59
ATOM	779	CB	ILE	215	9.561	19.420	63.133	1.00101.59
ATOM	780	CG2	ILE	215	9.891	20.656	63.989	1.00101.59
ATOM	781	CG1	ILE	215	10.536	19.201	61.965	1.00101.59
ATOM	782	CD1	ILE	215	10.425	20.268	60.876	1.00101.59
ATOM	783	C	ILE	215	10.905	18.140	64.654	1.00101.59
ATOM	784	O	ILE	215	11.780	17.444	64.142	1.00101.59
ATOM	785	N	LEU	216	11.122	18.846	65.777	1.00 71.07
ATOM	786	CA	LEU	216	12.441	19.086	66.298	1.00 71.07
ATOM	787	CB	LEU	216	12.443	19.971	67.554	1.00 71.07

ATOM	788	CG	LEU	216	11.974	21.411	67.274	1.00	71.07
ATOM	789	CD2	LEU	216	12.717	22.018	66.072	1.00	71.07
ATOM	790	CD1	LEU	216	12.062	22.281	68.538	1.00	71.07
ATOM	791	C	LEU	216	13.245	17.858	66.614	1.00	71.07
ATOM	792	O	LEU	216	14.434	17.832	66.307	1.00	71.07
ATOM	793	N	SER	217	12.668	16.807	67.217	1.00	91.67
ATOM	794	CA	SER	217	13.489	15.691	67.605	1.00	91.67
ATOM	795	CB	SER	217	12.686	14.580	68.299	1.00	91.67
ATOM	796	OG	SER	217	11.706	14.060	67.415	1.00	91.67
ATOM	797	C	SER	217	14.146	15.102	66.396	1.00	91.67
ATOM	798	O	SER	217	15.287	14.648	66.461	1.00	91.67
ATOM	799	N	TYR	218	13.450	15.117	65.249	1.00	91.93
ATOM	800	CA	TYR	218	13.967	14.526	64.052	1.00	91.93
ATOM	801	CB	TYR	218	12.965	14.580	62.887	1.00	91.93
ATOM	802	CG	TYR	218	13.598	13.904	61.723	1.00	91.93
ATOM	803	CD1	TYR	218	13.594	12.531	61.639	1.00	91.93
ATOM	804	CD2	TYR	218	14.187	14.636	60.716	1.00	91.93
ATOM	805	CE1	TYR	218	14.172	11.891	60.569	1.00	91.93
ATOM	806	CE2	TYR	218	14.768	14.000	59.643	1.00	91.93
ATOM	807	CZ	TYR	218	14.759	12.628	59.569	1.00	91.93
ATOM	808	OH	TYR	218	15.351	11.972	58.470	1.00	91.93
ATOM	809	C	TYR	218	15.220	15.241	63.624	1.00	91.93
ATOM	810	O	TYR	218	16.187	14.600	63.215	1.00	91.93
ATOM	811	N	ILE	219	15.247	16.586	63.726	1.00	130.52
ATOM	812	CA	ILE	219	16.367	17.377	63.277	1.00	130.52
ATOM	813	CB	ILE	219	16.191	18.863	63.444	1.00	130.52
ATOM	814	CG2	ILE	219	16.362	19.210	64.932	1.00	130.52
ATOM	815	CG1	ILE	219	17.184	19.615	62.541	1.00	130.52
ATOM	816	CD1	ILE	219	16.896	19.452	61.050	1.00	130.52
ATOM	817	C	ILE	219	17.573	16.969	64.061	1.00	130.52
ATOM	818	O	ILE	219	18.698	17.008	63.569	1.00	130.52
ATOM	819	N	LEU	220	17.348	16.588	65.328	1.00	154.16
ATOM	820	CA	LEU	220	18.369	16.162	66.239	1.00	154.16
ATOM	821	CB	LEU	220	17.799	15.834	67.629	1.00	154.16
ATOM	822	CG	LEU	220	18.840	15.357	68.658	1.00	154.16
ATOM	823	CD2	LEU	220	18.145	14.815	69.913	1.00	154.16
ATOM	824	CD1	LEU	220	19.877	16.451	68.974	1.00	154.16
ATOM	825	C	LEU	220	18.998	14.921	65.676	1.00	154.16
ATOM	826	O	LEU	220	20.148	14.608	65.984	1.00	154.16
ATOM	827	N	LYS	221	18.239	14.166	64.850	1.00	116.78
ATOM	828	CA	LYS	221	18.713	12.951	64.248	1.00	116.78
ATOM	829	CB	LYS	221	20.010	13.104	63.431	1.00	116.78
ATOM	830	CG	LYS	221	19.781	13.446	61.955	1.00	116.78
ATOM	831	CD	LYS	221	19.173	14.823	61.684	1.00	116.78
ATOM	832	CE	LYS	221	18.960	15.100	60.193	1.00	116.78
ATOM	833	NZ	LYS	221	18.364	16.442	60.003	1.00	116.78
ATOM	834	C	LYS	221	18.933	11.916	65.294	1.00	116.78
ATOM	835	O	LYS	221	19.776	11.032	65.143	1.00	116.78
ATOM	836	N	ASP	222	18.163	11.994	66.391	1.00	95.70
ATOM	837	CA	ASP	222	18.285	10.985	67.390	1.00	95.70
ATOM	838	CB	ASP	222	19.088	11.446	68.619	1.00	95.70
ATOM	839	CG	ASP	222	19.764	10.227	69.239	1.00	95.70
ATOM	840	OD1	ASP	222	19.230	9.095	69.101	1.00	95.70
ATOM	841	OD2	ASP	222	20.850	10.418	69.847	1.00	95.70
ATOM	842	C	ASP	222	16.884	10.667	67.806	1.00	95.70
ATOM	843	O	ASP	222	15.936	11.314	67.355	1.00	95.70
ATOM	844	N	LYS	223	16.713	9.632	68.651	1.00	73.05
ATOM	845	CA	LYS	223	15.410	9.247	69.104	1.00	73.05
ATOM	846	CB	LYS	223	15.081	7.777	68.786	1.00	73.05
ATOM	847	CG	LYS	223	14.980	7.499	67.283	1.00	73.05
ATOM	848	CD	LYS	223	14.994	6.012	66.915	1.00	73.05
ATOM	849	CE	LYS	223	16.395	5.438	66.695	1.00	73.05
ATOM	850	NZ	LYS	223	16.301	4.004	66.340	1.00	73.05
ATOM	851	C	LYS	223	15.387	9.406	70.594	1.00	73.05
ATOM	852	O	LYS	223	16.419	9.335	71.254	1.00	73.05
ATOM	853	N	ILE	224	14.179	9.594	71.156	1.00	70.41

ATOM	854	CA	ILE	224	13.955	9.832	72.556	1.00	70.41
ATOM	855	CB	ILE	224	12.504	10.030	72.899	1.00	70.41
ATOM	856	CG2	ILE	224	11.747	8.727	72.591	1.00	70.41
ATOM	857	CG1	ILE	224	12.359	10.508	74.355	1.00	70.41
ATOM	858	CD1	ILE	224	10.944	10.955	74.720	1.00	70.41
ATOM	859	C	ILE	224	14.450	8.672	73.367	1.00	70.41
ATOM	860	O	ILE	224	14.951	8.850	74.474	1.00	70.41
ATOM	861	N	LYS	225	14.307	7.443	72.851	1.00	97.06
ATOM	862	CA	LYS	225	14.661	6.273	73.604	1.00	97.06
ATOM	863	CB	LYS	225	14.480	4.980	72.798	1.00	97.06
ATOM	864	CG	LYS	225	13.054	4.737	72.315	1.00	97.06
ATOM	865	CD	LYS	225	12.965	3.668	71.226	1.00	97.06
ATOM	866	CE	LYS	225	12.377	2.339	71.707	1.00	97.06
ATOM	867	NZ	LYS	225	13.256	1.731	72.729	1.00	97.06
ATOM	868	C	LYS	225	16.112	6.313	73.984	1.00	97.06
ATOM	869	O	LYS	225	16.470	5.922	75.093	1.00	97.06
ATOM	870	N	SER	226	16.990	6.764	73.069	1.00	90.97
ATOM	871	CA	SER	226	18.410	6.730	73.291	1.00	90.97
ATOM	872	CB	SER	226	19.215	6.979	72.004	1.00	90.97
ATOM	873	OG	SER	226	20.605	6.933	72.287	1.00	90.97
ATOM	874	C	SER	226	18.870	7.741	74.308	1.00	90.97
ATOM	875	O	SER	226	19.916	7.548	74.922	1.00	90.97
ATOM	876	N	SER	227	18.108	8.833	74.522	1.00	110.32
ATOM	877	CA	SER	227	18.499	9.964	75.332	1.00	110.32
ATOM	878	CB	SER	227	17.489	11.119	75.265	1.00	110.32
ATOM	879	OG	SER	227	17.924	12.201	76.073	1.00	110.32
ATOM	880	C	SER	227	18.633	9.705	76.797	1.00	110.32
ATOM	881	O	SER	227	17.830	9.000	77.407	1.00	110.32
ATOM	882	N	THR	228	19.720	10.255	77.385	1.00	135.76
ATOM	883	CA	THR	228	19.856	10.302	78.811	1.00	135.76
ATOM	884	CB	THR	228	21.272	10.507	79.277	1.00	135.76
ATOM	885	OG1	THR	228	21.325	10.466	80.694	1.00	135.76
ATOM	886	CG2	THR	228	21.813	11.846	78.754	1.00	135.76
ATOM	887	C	THR	228	19.027	11.446	79.317	1.00	135.76
ATOM	888	O	THR	228	18.300	11.315	80.302	1.00	135.76
ATOM	889	N	SER	229	19.099	12.611	78.627	1.00	65.15
ATOM	890	CA	SER	229	18.361	13.736	79.125	1.00	65.15
ATOM	891	CB	SER	229	19.084	14.485	80.257	1.00	65.15
ATOM	892	OG	SER	229	19.237	13.627	81.380	1.00	65.15
ATOM	893	C	SER	229	18.107	14.715	78.024	1.00	65.15
ATOM	894	O	SER	229	18.783	14.717	76.997	1.00	65.15
ATOM	895	N	ARG	230	17.077	15.563	78.221	1.00	127.75
ATOM	896	CA	ARG	230	16.743	16.612	77.300	1.00	127.75
ATOM	897	CB	ARG	230	15.367	16.447	76.627	1.00	127.75
ATOM	898	CG	ARG	230	15.036	17.576	75.646	1.00	127.75
ATOM	899	CD	ARG	230	13.546	17.698	75.313	1.00	127.75
ATOM	900	NE	ARG	230	12.897	18.416	76.447	1.00	127.75
ATOM	901	CZ	ARG	230	12.371	17.715	77.493	1.00	127.75
ATOM	902	NH1	ARG	230	12.392	16.351	77.471	1.00	127.75
ATOM	903	NH2	ARG	230	11.832	18.376	78.560	1.00	127.75
ATOM	904	C	ARG	230	16.645	17.861	78.123	1.00	127.75
ATOM	905	O	ARG	230	15.977	17.874	79.157	1.00	127.75
ATOM	906	N	PHE	231	17.305	18.954	77.685	1.00	65.40
ATOM	907	CA	PHE	231	17.235	20.164	78.456	1.00	65.40
ATOM	908	CB	PHE	231	18.604	20.799	78.762	1.00	65.40
ATOM	909	CG	PHE	231	19.378	19.907	79.674	1.00	65.40
ATOM	910	CD1	PHE	231	20.144	18.876	79.175	1.00	65.40
ATOM	911	CD2	PHE	231	19.351	20.109	81.034	1.00	65.40
ATOM	912	CE1	PHE	231	20.861	18.059	80.020	1.00	65.40
ATOM	913	CE2	PHE	231	20.064	19.295	81.882	1.00	65.40
ATOM	914	CZ	PHE	231	20.824	18.268	81.377	1.00	65.40
ATOM	915	C	PHE	231	16.455	21.183	77.681	1.00	65.40
ATOM	916	O	PHE	231	16.590	21.284	76.464	1.00	65.40
ATOM	917	N	VAL	232	15.583	21.955	78.365	1.00	54.92
ATOM	918	CA	VAL	232	14.876	22.976	77.648	1.00	54.92
ATOM	919	CB	VAL	232	13.409	22.698	77.490	1.00	54.92

ATOM	920	CG1	VAL	232	12.754	23.898	76.786	1.00 54.92
ATOM	921	CG2	VAL	232	13.244	21.370	76.736	1.00 54.92
ATOM	922	C	VAL	232	15.011	24.260	78.404	1.00 54.92
ATOM	923	O	VAL	232	14.491	24.399	79.511	1.00 54.92
ATOM	924	N	MET	233	15.697	25.250	77.798	1.00161.31
ATOM	925	CA	MET	233	15.841	26.540	78.406	1.00161.31
ATOM	926	CB	MET	233	16.866	27.450	77.708	1.00161.31
ATOM	927	CG	MET	233	18.319	27.051	77.977	1.00161.31
ATOM	928	SD	MET	233	18.818	25.457	77.264	1.00161.31
ATOM	929	CE	MET	233	18.262	24.451	78.667	1.00161.31
ATOM	930	C	MET	233	14.501	27.185	78.306	1.00161.31
ATOM	931	O	MET	233	13.759	26.978	77.345	1.00161.31
ATOM	932	N	PHE	234	14.169	27.997	79.320	1.00157.04
ATOM	933	CA	PHE	234	12.858	28.548	79.456	1.00157.04
ATOM	934	CB	PHE	234	12.307	28.180	80.844	1.00157.04
ATOM	935	CG	PHE	234	10.873	28.528	80.992	1.00157.04
ATOM	936	CD1	PHE	234	10.467	29.841	81.006	1.00157.04
ATOM	937	CD2	PHE	234	9.932	27.532	81.104	1.00157.04
ATOM	938	CE1	PHE	234	9.138	30.162	81.142	1.00157.04
ATOM	939	CE2	PHE	234	8.605	27.851	81.243	1.00157.04
ATOM	940	CZ	PHE	234	8.202	29.165	81.262	1.00157.04
ATOM	941	C	PHE	234	12.977	30.035	79.439	1.00157.04
ATOM	942	O	PHE	234	13.862	30.610	80.072	1.00157.04
ATOM	943	N	GLY	235	12.069	30.702	78.707	1.00 36.60
ATOM	944	CA	GLY	235	12.071	32.130	78.725	1.00 36.60
ATOM	945	C	GLY	235	10.788	32.496	79.392	1.00 36.60
ATOM	946	O	GLY	235	9.740	31.923	79.098	1.00 36.60
ATOM	947	N	PHE	236	10.847	33.476	80.310	1.00124.45
ATOM	948	CA	PHE	236	9.688	33.908	81.033	1.00124.45
ATOM	949	CB	PHE	236	10.025	34.424	82.451	1.00124.45
ATOM	950	CG	PHE	236	8.777	34.878	83.134	1.00124.45
ATOM	951	CD1	PHE	236	7.844	33.978	83.598	1.00124.45
ATOM	952	CD2	PHE	236	8.552	36.220	83.328	1.00124.45
ATOM	953	CE1	PHE	236	6.701	34.418	84.226	1.00124.45
ATOM	954	CE2	PHE	236	7.412	36.666	83.956	1.00124.45
ATOM	955	CZ	PHE	236	6.480	35.762	84.406	1.00124.45
ATOM	956	C	PHE	236	9.074	35.005	80.228	1.00124.45
ATOM	957	O	PHE	236	9.718	35.532	79.322	1.00124.45
ATOM	958	N	CYS	237	7.805	35.361	80.530	1.00168.32
ATOM	959	CA	CYS	237	7.128	36.378	79.777	1.00168.32
ATOM	960	CB	CYS	237	5.751	36.753	80.352	1.00168.32
ATOM	961	SG	CYS	237	4.549	35.394	80.243	1.00168.32
ATOM	962	C	CYS	237	7.986	37.583	79.865	1.00168.32
ATOM	963	O	CYS	237	8.268	38.226	78.854	1.00168.32
ATOM	964	N	TYR	238	8.442	37.926	81.081	1.00284.30
ATOM	965	CA	TYR	238	9.416	38.961	81.072	1.00284.30
ATOM	966	CB	TYR	238	9.903	39.425	82.462	1.00284.30
ATOM	967	CG	TYR	238	8.854	40.286	83.078	1.00284.30
ATOM	968	CD1	TYR	238	8.763	41.610	82.716	1.00284.30
ATOM	969	CD2	TYR	238	7.978	39.791	84.017	1.00284.30
ATOM	970	CE1	TYR	238	7.806	42.429	83.266	1.00284.30
ATOM	971	CE2	TYR	238	7.018	40.607	84.574	1.00284.30
ATOM	972	CZ	TYR	238	6.932	41.927	84.199	1.00284.30
ATOM	973	OH	TYR	238	5.948	42.765	84.766	1.00284.30
ATOM	974	C	TYR	238	10.554	38.314	80.372	1.00284.30
ATOM	975	O	TYR	238	10.991	37.226	80.741	1.00284.30
ATOM	976	N	LEU	239	11.055	38.973	79.320	1.00171.87
ATOM	977	CA	LEU	239	12.103	38.407	78.536	1.00171.87
ATOM	978	CB	LEU	239	12.501	39.289	77.341	1.00171.87
ATOM	979	CG	LEU	239	12.683	40.775	77.715	1.00171.87
ATOM	980	CD2	LEU	239	11.503	41.296	78.551	1.00171.87
ATOM	981	CD1	LEU	239	12.953	41.633	76.469	1.00171.87
ATOM	982	C	LEU	239	13.273	38.263	79.446	1.00171.87
ATOM	983	O	LEU	239	14.132	37.407	79.253	1.00171.87
ATOM	984	N	SER	240	13.308	39.118	80.478	1.00119.68
ATOM	985	CA	SER	240	14.403	39.216	81.390	1.00119.68

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ATOM    986  CB  SER   240      14.206  40.338  82.423  1.00119.68
ATOM    987  OG  SER   240      15.316  40.390  83.307  1.00119.68
ATOM    988  C   SER   240      14.663  37.940  82.151  1.00119.68
ATOM    989  O   SER   240      15.794  37.735  82.584  1.00119.68
ATOM    990  N   HIS   241      13.682  37.034  82.352  1.00100.43
ATOM    991  CA  HIS   241      14.003  35.901  83.190  1.00100.43
ATOM    992  ND1 HIS   241      13.297  33.116  84.774  1.00100.43
ATOM    993  CG  HIS   241      13.303  34.445  85.135  1.00100.43
ATOM    994  CB  HIS   241      12.906  35.559  84.213  1.00100.43
ATOM    995  NE2 HIS   241      14.003  33.198  86.881  1.00100.43
ATOM    996  CD2 HIS   241      13.736  34.477  86.425  1.00100.43
ATOM    997  CE1 HIS   241      13.724  32.415  85.855  1.00100.43
ATOM    998  C   HIS   241      14.250  34.656  82.382  1.00100.43
ATOM    999  O   HIS   241      13.594  34.412  81.371  1.00100.43
ATOM   1000  N   TRP   242      15.237  33.839  82.828  1.00 71.70
ATOM   1001  CA  TRP   242      15.568  32.596  82.183  1.00 71.70
ATOM   1002  CB  TRP   242      16.978  32.577  81.559  1.00 71.70
ATOM   1003  CG  TRP   242      17.211  31.501  80.518  1.00 71.70
ATOM   1004  CD2 TRP   242      16.960  30.110  80.750  1.00 71.70
ATOM   1005  CD1 TRP   242      17.689  31.602  79.246  1.00 71.70
ATOM   1006  NE1 TRP   242      17.753  30.353  78.668  1.00 71.70
ATOM   1007  CE2 TRP   242      17.306  29.425  79.588  1.00 71.70
ATOM   1008  CE3 TRP   242      16.483  29.452  81.849  1.00 71.70
ATOM   1009  CZ2 TRP   242      17.180  28.067  79.501  1.00 71.70
ATOM   1010  CZ3 TRP   242      16.352  28.085  81.760  1.00 71.70
ATOM   1011  CH2 TRP   242      16.694  27.406  80.610  1.00 71.70
ATOM   1012  C   TRP   242      15.543  31.511  83.223  1.00 71.70
ATOM   1013  O   TRP   242      16.038  31.691  84.334  1.00 71.70
ATOM   1014  N   LYS   243      14.954  30.348  82.873  1.00134.01
ATOM   1015  CA  LYS   243      14.840  29.232  83.772  1.00134.01
ATOM   1016  CB  LYS   243      13.473  29.195  84.481  1.00134.01
ATOM   1017  CG  LYS   243      12.291  29.385  83.532  1.00134.01
ATOM   1018  CD  LYS   243      10.931  29.354  84.229  1.00134.01
ATOM   1019  CE  LYS   243      10.595  30.669  84.937  1.00134.01
ATOM   1020  NZ  LYS   243       9.215  30.623  85.468  1.00134.01
ATOM   1021  C   LYS   243      15.057  27.987  82.960  1.00134.01
ATOM   1022  O   LYS   243      15.282  28.077  81.755  1.00134.01
ATOM   1023  N   CYS   244      15.048  26.787  83.586  1.00 62.56
ATOM   1024  CA  CYS   244      15.340  25.638  82.771  1.00 62.56
ATOM   1025  CB  CYS   244      16.815  25.213  82.855  1.00 62.56
ATOM   1026  SG  CYS   244      17.198  23.765  81.826  1.00 62.56
ATOM   1027  C   CYS   244      14.518  24.452  83.180  1.00 62.56
ATOM   1028  O   CYS   244      14.132  24.296  84.337  1.00 62.56
ATOM   1029  N   VAL   245      14.220  23.573  82.204  1.00105.02
ATOM   1030  CA  VAL   245      13.522  22.360  82.509  1.00105.02
ATOM   1031  CB  VAL   245      12.237  22.162  81.758  1.00105.02
ATOM   1032  CG1 VAL   245      11.241  23.250  82.186  1.00105.02
ATOM   1033  CG2 VAL   245      12.541  22.149  80.254  1.00105.02
ATOM   1034  C   VAL   245      14.437  21.242  82.137  1.00105.02
ATOM   1035  O   VAL   245      15.161  21.330  81.145  1.00105.02
ATOM   1036  N   ILE   246      14.469  20.170  82.956  1.00 69.99
ATOM   1037  CA  ILE   246      15.311  19.068  82.601  1.00 69.99
ATOM   1038  CB  ILE   246      16.362  18.704  83.605  1.00 69.99
ATOM   1039  CG2 ILE   246      17.040  17.415  83.114  1.00 69.99
ATOM   1040  CG1 ILE   246      17.357  19.840  83.845  1.00 69.99
ATOM   1041  CD1 ILE   246      18.356  19.453  84.928  1.00 69.99
ATOM   1042  C   ILE   246      14.466  17.845  82.536  1.00 69.99
ATOM   1043  O   ILE   246      13.752  17.519  83.483  1.00 69.99
ATOM   1044  N   TYR   247      14.526  17.118  81.409  1.00162.63
ATOM   1045  CA  TYR   247      13.821  15.877  81.419  1.00162.63
ATOM   1046  CB  TYR   247      12.993  15.571  80.164  1.00162.63
ATOM   1047  CG  TYR   247      12.404  14.225  80.410  1.00162.63
ATOM   1048  CD1 TYR   247      11.304  14.083  81.227  1.00162.63
ATOM   1049  CD2 TYR   247      12.952  13.106  79.831  1.00162.63
ATOM   1050  CE1 TYR   247      10.760  12.842  81.461  1.00162.63
ATOM   1051  CE2 TYR   247      12.411  11.864  80.062  1.00162.63
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ATOM   1052  CZ  TYR   247      11.313  11.730  80.876  1.00162.63
ATOM   1053  OH  TYR   247      10.760  10.453  81.111  1.00162.63
ATOM   1054  C   TYR   247      14.873  14.832  81.502  1.00162.63
ATOM   1055  O   TYR   247      15.725  14.720  80.623  1.00162.63
ATOM   1056  N   ASP   248      14.861  14.054  82.598  1.00120.84
ATOM   1057  CA  ASP   248      15.853  13.040  82.731  1.00120.84
ATOM   1058  CB  ASP   248      16.545  13.029  84.105  1.00120.84
ATOM   1059  CG  ASP   248      15.489  12.886  85.182  1.00120.84
ATOM   1060  OD1 ASP   248      15.119  11.728  85.497  1.00120.84
ATOM   1061  OD2 ASP   248      15.045  13.937  85.714  1.00120.84
ATOM   1062  C   ASP   248      15.220  11.721  82.447  1.00120.84
ATOM   1063  O   ASP   248      14.346  11.239  83.161  1.00120.84
ATOM   1064  N   LYS   249      15.627  11.115  81.325  1.00137.23
ATOM   1065  CA  LYS   249      15.099   9.839  80.954  1.00137.23
ATOM   1066  CB  LYS   249      15.586   9.390  79.563  1.00137.23
ATOM   1067  CG  LYS   249      15.422   7.890  79.295  1.00137.23
ATOM   1068  CD  LYS   249      13.983   7.378  79.300  1.00137.23
ATOM   1069  CE  LYS   249      13.903   5.865  79.081  1.00137.23
ATOM   1070  NZ  LYS   249      12.538   5.377  79.380  1.00137.23
ATOM   1071  C   LYS   249      15.536   8.806  81.941  1.00137.23
ATOM   1072  O   LYS   249      14.751   7.941  82.325  1.00137.23
ATOM   1073  N   LYS   250      16.810   8.864  82.375  1.00140.70
ATOM   1074  CA  LYS   250      17.312   7.828  83.232  1.00140.70
ATOM   1075  CB  LYS   250      18.817   7.965  83.526  1.00140.70
ATOM   1076  CG  LYS   250      19.206   9.188  84.359  1.00140.70
ATOM   1077  CD  LYS   250      20.614   9.087  84.948  1.00140.70
ATOM   1078  CE  LYS   250      21.722   9.373  83.934  1.00140.70
ATOM   1079  NZ  LYS   250      21.855  10.833  83.730  1.00140.70
ATOM   1080  C   LYS   250      16.603   7.804  84.555  1.00140.70
ATOM   1081  O   LYS   250      16.115   6.759  84.982  1.00140.70
ATOM   1082  N   GLN   251      16.534   8.962  85.239  1.00123.46
ATOM   1083  CA  GLN   251      15.928   9.069  86.537  1.00123.46
ATOM   1084  CB  GLN   251      16.416  10.269  87.378  1.00123.46
ATOM   1085  CG  GLN   251      15.776  10.383  88.762  1.00123.46
ATOM   1086  CD  GLN   251      16.494  11.496  89.518  1.00123.46
ATOM   1087  OE1 GLN   251      15.986  12.034  90.499  1.00123.46
ATOM   1088  NE2 GLN   251      17.723  11.844  89.053  1.00123.46
ATOM   1089  C   GLN   251      14.433   9.026  86.417  1.00123.46
ATOM   1090  O   GLN   251      13.737   8.731  87.387  1.00123.46
ATOM   1091  N   CYS   252      13.900   9.307  85.212  1.00 57.14
ATOM   1092  CA  CYS   252      12.481   9.332  85.003  1.00 57.14
ATOM   1093  CB  CYS   252      11.792   8.009  85.384  1.00 57.14
ATOM   1094  SG  CYS   252      12.283   6.624  84.314  1.00 57.14
ATOM   1095  C   CYS   252      11.864  10.429  85.808  1.00 57.14
ATOM   1096  O   CYS   252      10.816  10.259  86.429  1.00 57.14
ATOM   1097  N   LEU   253      12.527  11.600  85.826  1.00 58.16
ATOM   1098  CA  LEU   253      11.977  12.742  86.490  1.00 58.16
ATOM   1099  CB  LEU   253      12.742  13.160  87.761  1.00 58.16
ATOM   1100  CG  LEU   253      12.666  12.118  88.897  1.00 58.16
ATOM   1101  CD2 LEU   253      11.225  11.641  89.125  1.00 58.16
ATOM   1102  CD1 LEU   253      13.328  12.646  90.181  1.00 58.16
ATOM   1103  C   LEU   253      11.998  13.897  85.533  1.00 58.16
ATOM   1104  O   LEU   253      12.768  13.915  84.572  1.00 58.16
ATOM   1105  N   VAL   254      11.093  14.870  85.756  1.00 54.62
ATOM   1106  CA  VAL   254      11.055  16.079  84.986  1.00 54.62
ATOM   1107  CB  VAL   254       9.737  16.349  84.318  1.00 54.62
ATOM   1108  CG1 VAL   254       9.768  17.773  83.745  1.00 54.62
ATOM   1109  CG2 VAL   254       9.498  15.270  83.249  1.00 54.62
ATOM   1110  C   VAL   254      11.251  17.154  85.994  1.00 54.62
ATOM   1111  O   VAL   254      10.523  17.214  86.985  1.00 54.62
ATOM   1112  N   SER   255      12.232  18.045  85.775  1.00 89.13
ATOM   1113  CA  SER   255      12.477  18.995  86.812  1.00 89.13
ATOM   1114  CB  SER   255      13.855  18.822  87.471  1.00 89.13
ATOM   1115  OG  SER   255      13.919  17.580  88.156  1.00 89.13
ATOM   1116  C   SER   255      12.418  20.377  86.264  1.00 89.13
ATOM   1117  O   SER   255      12.668  20.611  85.081  1.00 89.13
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ATOM	1118	N	PHE	256	12.042	21.321	87.151	1.00 81.52
ATOM	1119	CA	PHE	256	11.974	22.719	86.856	1.00 81.52
ATOM	1120	CB	PHE	256	10.587	23.303	87.192	1.00 81.52
ATOM	1121	CG	PHE	256	10.553	24.775	86.949	1.00 81.52
ATOM	1122	CD1	PHE	256	10.544	25.283	85.670	1.00 81.52
ATOM	1123	CD2	PHE	256	10.493	25.650	88.011	1.00 81.52
ATOM	1124	CE1	PHE	256	10.502	26.641	85.457	1.00 81.52
ATOM	1125	CE2	PHE	256	10.450	27.009	87.805	1.00 81.52
ATOM	1126	CZ	PHE	256	10.457	27.507	86.524	1.00 81.52
ATOM	1127	C	PHE	256	12.995	23.343	87.754	1.00 81.52
ATOM	1128	O	PHE	256	12.908	23.224	88.974	1.00 81.52
ATOM	1129	N	TYR	257	13.991	24.020	87.148	1.00150.24
ATOM	1130	CA	TYR	257	15.109	24.629	87.809	1.00150.24
ATOM	1131	CB	TYR	257	16.428	24.122	87.204	1.00150.24
ATOM	1132	CG	TYR	257	17.512	25.123	87.394	1.00150.24
ATOM	1133	CD1	TYR	257	18.208	25.218	88.567	1.00150.24
ATOM	1134	CD2	TYR	257	17.837	25.972	86.361	1.00150.24
ATOM	1135	CE1	TYR	257	19.206	26.151	88.715	1.00150.24
ATOM	1136	CE2	TYR	257	18.832	26.908	86.498	1.00150.24
ATOM	1137	CZ	TYR	257	19.522	26.996	87.681	1.00150.24
ATOM	1138	OH	TYR	257	20.546	27.950	87.840	1.00150.24
ATOM	1139	C	TYR	257	15.053	26.098	87.599	1.00150.24
ATOM	1140	O	TYR	257	15.127	26.570	86.467	1.00150.24
ATOM	1141	N	ASP	258	14.945	26.863	88.706	1.00 96.85
ATOM	1142	CA	ASP	258	14.800	28.282	88.571	1.00 96.85
ATOM	1143	CB	ASP	258	13.335	28.709	88.797	1.00 96.85
ATOM	1144	CG	ASP	258	13.113	30.119	88.281	1.00 96.85
ATOM	1145	OD1	ASP	258	14.109	30.883	88.199	1.00 96.85
ATOM	1146	OD2	ASP	258	11.941	30.448	87.958	1.00 96.85
ATOM	1147	C	ASP	258	15.644	28.937	89.624	1.00 96.85
ATOM	1148	O	ASP	258	15.412	28.753	90.817	1.00 96.85
ATOM	1149	N	SER	259	16.665	29.708	89.204	1.00 85.86
ATOM	1150	CA	SER	259	17.530	30.407	90.117	1.00 85.86
ATOM	1151	CB	SER	259	18.781	30.984	89.432	1.00 85.86
ATOM	1152	OG	SER	259	18.407	31.895	88.409	1.00 85.86
ATOM	1153	C	SER	259	16.768	31.549	90.718	1.00 85.86
ATOM	1154	O	SER	259	17.222	32.172	91.678	1.00 85.86
ATOM	1155	N	GLY	260	15.605	31.865	90.112	1.00113.20
ATOM	1156	CA	GLY	260	14.706	32.930	90.474	1.00113.20
ATOM	1157	C	GLY	260	14.045	32.686	91.792	1.00113.20
ATOM	1158	O	GLY	260	13.764	33.636	92.515	1.00113.20
ATOM	1159	N	GLY	261	13.720	31.424	92.130	1.00 86.72
ATOM	1160	CA	GLY	261	13.064	31.199	93.385	1.00 86.72
ATOM	1161	C	GLY	261	11.592	31.341	93.186	1.00 86.72
ATOM	1162	O	GLY	261	11.067	30.999	92.130	1.00 86.72
ATOM	1163	N	ASN	262	10.881	31.879	94.198	1.00207.82
ATOM	1164	CA	ASN	262	9.456	31.925	94.083	1.00207.82
ATOM	1165	CB	ASN	262	8.966	32.726	92.860	1.00207.82
ATOM	1166	CG	ASN	262	9.258	34.208	93.079	1.00207.82
ATOM	1167	OD1	ASN	262	9.119	34.718	94.189	1.00207.82
ATOM	1168	ND2	ASN	262	9.670	34.916	91.994	1.00207.82
ATOM	1169	C	ASN	262	9.035	30.503	93.904	1.00207.82
ATOM	1170	O	ASN	262	8.251	30.184	93.012	1.00207.82
ATOM	1171	N	ILE	263	9.571	29.630	94.787	1.00193.31
ATOM	1172	CA	ILE	263	9.388	28.206	94.792	1.00193.31
ATOM	1173	CB	ILE	263	9.688	27.587	96.127	1.00193.31
ATOM	1174	CG2	ILE	263	8.780	28.259	97.166	1.00193.31
ATOM	1175	CG1	ILE	263	9.539	26.058	96.070	1.00193.31
ATOM	1176	CD1	ILE	263	10.598	25.377	95.202	1.00193.31
ATOM	1177	C	ILE	263	7.983	27.869	94.442	1.00193.31
ATOM	1178	O	ILE	263	7.026	28.491	94.897	1.00193.31
ATOM	1179	N	PRO	264	7.860	26.906	93.580	1.00100.94
ATOM	1180	CA	PRO	264	6.545	26.501	93.191	1.00100.94
ATOM	1181	CD	PRO	264	8.797	26.817	92.472	1.00100.94
ATOM	1182	CB	PRO	264	6.707	25.738	91.886	1.00100.94
ATOM	1183	CG	PRO	264	7.964	26.365	91.262	1.00100.94

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ATOM   1184  C   PRO   264       5.889  25.722  94.276  1.00100.94
ATOM   1185  O   PRO   264       6.579  25.112  95.091  1.00100.94
ATOM   1186  N   THR   265       4.550  25.758  94.313  1.00232.51
ATOM   1187  CA  THR   265       3.808  25.043  95.300  1.00232.51
ATOM   1188  CB  THR   265       3.702  25.797  96.601  1.00232.51
ATOM   1189  OG1 THR   265       3.098  24.996  97.606  1.00232.51
ATOM   1190  CG2 THR   265       2.911  27.097  96.380  1.00232.51
ATOM   1191  C   THR   265       2.453  24.873  94.706  1.00232.51
ATOM   1192  O   THR   265       2.308  24.753  93.489  1.00232.51
ATOM   1193  N   GLU   266       1.419  24.847  95.556  1.00 72.96
ATOM   1194  CA  GLU   266       0.090  24.777  95.058  1.00 72.96
ATOM   1195  CB  GLU   266      -0.973  24.865  96.163  1.00 72.96
ATOM   1196  CG  GLU   266      -0.967  23.675  97.125  1.00 72.96
ATOM   1197  CD  GLU   266      -2.060  23.897  98.160  1.00 72.96
ATOM   1198  OE1 GLU   266      -3.191  24.275  97.757  1.00 72.96
ATOM   1199  OE2 GLU   266      -1.776  23.693  99.371  1.00 72.96
ATOM   1200  C   GLU   266      -0.048  26.011  94.241  1.00 72.96
ATOM   1201  O   GLU   266      -0.736  26.023  93.223  1.00 72.96
ATOM   1202  N   PHE   267       0.662  27.073  94.666  1.00 75.25
ATOM   1203  CA  PHE   267       0.549  28.365  94.062  1.00 75.25
ATOM   1204  CB  PHE   267       1.597  29.354  94.601  1.00 75.25
ATOM   1205  CG  PHE   267       1.160  30.739  94.260  1.00 75.25
ATOM   1206  CD1 PHE   267       0.265  31.380  95.082  1.00 75.25
ATOM   1207  CD2 PHE   267       1.637  31.400  93.151  1.00 75.25
ATOM   1208  CE1 PHE   267      -0.159  32.658  94.808  1.00 75.25
ATOM   1209  CE2 PHE   267       1.218  32.682  92.871  1.00 75.25
ATOM   1210  CZ  PHE   267       0.318  33.312  93.698  1.00 75.25
ATOM   1211  C   PHE   267       0.806  28.206  92.600  1.00 75.25
ATOM   1212  O   PHE   267      -0.005  28.644  91.785  1.00 75.25
ATOM   1213  N   HIS   268       1.926  27.569  92.209  1.00120.57
ATOM   1214  CA  HIS   268       2.071  27.374  90.801  1.00120.57
ATOM   1215  ND1 HIS   268       4.629  28.952  91.451  1.00120.57
ATOM   1216  CG  HIS   268       4.424  28.128  90.367  1.00120.57
ATOM   1217  CB  HIS   268       3.487  26.957  90.371  1.00120.57
ATOM   1218  NE2 HIS   268       5.893  29.745  89.801  1.00120.57
ATOM   1219  CD2 HIS   268       5.204  28.626  89.368  1.00120.57
ATOM   1220  CE1 HIS   268       5.514  29.902  91.057  1.00120.57
ATOM   1221  C   HIS   268       1.090  26.308  90.438  1.00120.57
ATOM   1222  O   HIS   268       0.964  25.311  91.144  1.00120.57
ATOM   1223  N   HIS   269       0.382  26.478  89.304  1.00285.66
ATOM   1224  CA  HIS   269      -0.638  25.533  88.947  1.00285.66
ATOM   1225  ND1 HIS   269      -1.508  22.985  86.957  1.00285.66
ATOM   1226  CG  HIS   269      -1.094  23.103  88.265  1.00285.66
ATOM   1227  CB  HIS   269      -0.088  24.110  88.745  1.00285.66
ATOM   1228  NE2 HIS   269      -2.589  21.420  88.112  1.00285.66
ATOM   1229  CD2 HIS   269      -1.765  22.141  88.955  1.00285.66
ATOM   1230  CE1 HIS   269      -2.403  21.963  86.922  1.00285.66
ATOM   1231  C   HIS   269      -1.663  25.496  90.041  1.00285.66
ATOM   1232  O   HIS   269      -2.053  24.430  90.513  1.00285.66
ATOM   1233  N   TYR   270      -2.135  26.680  90.480  1.00275.40
ATOM   1234  CA  TYR   270      -3.136  26.703  91.507  1.00275.40
ATOM   1235  CB  TYR   270      -2.831  27.685  92.652  1.00275.40
ATOM   1236  CG  TYR   270      -3.831  27.449  93.732  1.00275.40
ATOM   1237  CD1 TYR   270      -3.682  26.373  94.578  1.00275.40
ATOM   1238  CD2 TYR   270      -4.904  28.292  93.910  1.00275.40
ATOM   1239  CE1 TYR   270      -4.589  26.135  95.583  1.00275.40
ATOM   1240  CE2 TYR   270      -5.814  28.060  94.915  1.00275.40
ATOM   1241  CZ  TYR   270      -5.658  26.980  95.752  1.00275.40
ATOM   1242  OH  TYR   270      -6.591  26.743  96.784  1.00275.40
ATOM   1243  C   TYR   270      -4.386  27.189  90.857  1.00275.40
ATOM   1244  O   TYR   270      -4.368  28.183  90.132  1.00275.40
ATOM   1245  N   ASN   271      -5.513  26.488  91.082  1.00242.49
ATOM   1246  CA  ASN   271      -6.723  26.931  90.459  1.00242.49
ATOM   1247  CB  ASN   271      -7.903  25.953  90.624  1.00242.49
ATOM   1248  CG  ASN   271      -8.189  25.790  92.112  1.00242.49
ATOM   1249  OD1 ASN   271      -7.323  25.367  92.876  1.00242.49
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ATOM   1250  ND2 ASN   271      -9.431  26.143  92.537  1.00242.49
ATOM   1251  C   ASN   271      -7.092  28.242  91.067  1.00242.49
ATOM   1252  O   ASN   271      -7.266  28.364  92.279  1.00242.49
ATOM   1253  N   ASN   272      -7.182  29.279  90.218  1.00289.61
ATOM   1254  CA  ASN   272      -7.544  30.581  90.681  1.00289.61
ATOM   1255  CB  ASN   272      -6.612  31.124  91.781  1.00289.61
ATOM   1256  CG  ASN   272      -5.168  31.036  91.298  1.00289.61
ATOM   1257  OD1 ASN   272      -4.407  30.209  91.794  1.00289.61
ATOM   1258  ND2 ASN   272      -4.774  31.887  90.314  1.00289.61
ATOM   1259  C   ASN   272      -7.490  31.497  89.508  1.00289.61
ATOM   1260  O   ASN   272      -6.959  31.145  88.456  1.00289.61
ATOM   1261  N   PHE   273      -8.071  32.701  89.651  1.00223.87
ATOM   1262  CA  PHE   273      -7.991  33.613  88.555  1.00223.87
ATOM   1263  CB  PHE   273      -9.254  34.480  88.413  1.00223.87
ATOM   1264  CG  PHE   273      -9.184  35.214  87.119  1.00223.87
ATOM   1265  CD1 PHE   273      -9.640  34.621  85.963  1.00223.87
ATOM   1266  CD2 PHE   273      -8.669  36.488  87.053  1.00223.87
ATOM   1267  CE1 PHE   273      -9.584  35.284  84.761  1.00223.87
ATOM   1268  CE2 PHE   273      -8.611  37.156  85.852  1.00223.87
ATOM   1269  CZ  PHE   273      -9.068  36.556  84.703  1.00223.87
ATOM   1270  C   PHE   273      -6.857  34.529  88.874  1.00223.87
ATOM   1271  O   PHE   273      -7.064  35.676  89.266  1.00223.87
ATOM   1272  N   TYR   274      -5.615  34.038  88.712  1.00256.35
ATOM   1273  CA  TYR   274      -4.475  34.866  88.967  1.00256.35
ATOM   1274  CB  TYR   274      -3.716  34.548  90.268  1.00256.35
ATOM   1275  CG  TYR   274      -4.554  34.961  91.425  1.00256.35
ATOM   1276  CD1 TYR   274      -5.525  34.132  91.933  1.00256.35
ATOM   1277  CD2 TYR   274      -4.353  36.193  92.007  1.00256.35
ATOM   1278  CE1 TYR   274      -6.290  34.526  93.006  1.00256.35
ATOM   1279  CE2 TYR   274      -5.113  36.595  93.079  1.00256.35
ATOM   1280  CZ  TYR   274      -6.080  35.760  93.580  1.00256.35
ATOM   1281  OH  TYR   274      -6.862  36.167  94.680  1.00256.35
ATOM   1282  C   TYR   274      -3.500  34.635  87.867  1.00256.35
ATOM   1283  O   TYR   274      -3.453  33.556  87.277  1.00256.35
ATOM   1284  N   PHE   275      -2.699  35.667  87.550  1.00303.44
ATOM   1285  CA  PHE   275      -1.698  35.480  86.550  1.00303.44
ATOM   1286  CB  PHE   275      -1.587  36.682  85.587  1.00303.44
ATOM   1287  CG  PHE   275      -1.447  37.922  86.400  1.00303.44
ATOM   1288  CD1 PHE   275      -2.552  38.467  87.016  1.00303.44
ATOM   1289  CD2 PHE   275      -0.233  38.554  86.539  1.00303.44
ATOM   1290  CE1 PHE   275      -2.442  39.612  87.769  1.00303.44
ATOM   1291  CE2 PHE   275      -0.116  39.698  87.293  1.00303.44
ATOM   1292  CZ  PHE   275      -1.222  40.231  87.910  1.00303.44
ATOM   1293  C   PHE   275      -0.395  35.232  87.247  1.00303.44
ATOM   1294  O   PHE   275       0.256  36.148  87.747  1.00303.44
ATOM   1295  N   TYR   276      -0.001  33.947  87.316  1.00249.15
ATOM   1296  CA  TYR   276       1.246  33.560  87.901  1.00249.15
ATOM   1297  CB  TYR   276       1.157  33.083  89.363  1.00249.15
ATOM   1298  CG  TYR   276       1.040  34.282  90.245  1.00249.15
ATOM   1299  CD1 TYR   276      -0.159  34.928  90.435  1.00249.15
ATOM   1300  CD2 TYR   276       2.158  34.758  90.891  1.00249.15
ATOM   1301  CE1 TYR   276      -0.240  36.029  91.256  1.00249.15
ATOM   1302  CE2 TYR   276       2.086  35.857  91.713  1.00249.15
ATOM   1303  CZ  TYR   276       0.887  36.497  91.894  1.00249.15
ATOM   1304  OH  TYR   276       0.813  37.627  92.736  1.00249.15
ATOM   1305  C   TYR   276       1.775  32.444  87.073  1.00249.15
ATOM   1306  O   TYR   276       1.053  31.868  86.260  1.00249.15
ATOM   1307  N   SER   277       3.071  32.124  87.243  1.00212.61
ATOM   1308  CA  SER   277       3.655  31.079  86.459  1.00212.61
ATOM   1309  CB  SER   277       5.186  31.022  86.551  1.00212.61
ATOM   1310  OG  SER   277       5.676  29.934  85.782  1.00212.61
ATOM   1311  C   SER   277       3.147  29.777  86.954  1.00212.61
ATOM   1312  O   SER   277       2.899  29.589  88.143  1.00212.61
ATOM   1313  N   PHE   278       2.950  28.826  86.033  1.00225.57
ATOM   1314  CA  PHE   278       2.565  27.549  86.524  1.00225.57
ATOM   1315  CB  PHE   278       1.482  26.853  85.681  1.00225.57
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ATOM   1316  CG  PHE   278       0.264  27.710  85.688  1.00225.57
ATOM   1317  CD1 PHE   278      -0.538  27.793  86.804  1.00225.57
ATOM   1318  CD2 PHE   278      -0.085  28.421  84.564  1.00225.57
ATOM   1319  CE1 PHE   278      -1.663  28.585  86.801  1.00225.57
ATOM   1320  CE2 PHE   278      -1.209  29.212  84.555  1.00225.57
ATOM   1321  CZ  PHE   278      -2.000  29.297  85.676  1.00225.57
ATOM   1322  C   PHE   278       3.792  26.723  86.394  1.00225.57
ATOM   1323  O   PHE   278       4.126  26.285  85.296  1.00225.57
ATOM   1324  N   SER   279       4.509  26.495  87.509  1.00 63.44
ATOM   1325  CA  SER   279       5.684  25.695  87.383  1.00 63.44
ATOM   1326  CB  SER   279       6.414  25.459  88.712  1.00 63.44
ATOM   1327  OG  SER   279       5.673  24.541  89.502  1.00 63.44
ATOM   1328  C   SER   279       5.183  24.367  86.941  1.00 63.44
ATOM   1329  O   SER   279       5.805  23.687  86.126  1.00 63.44
ATOM   1330  N   ASP   280       4.011  23.979  87.478  1.00 78.81
ATOM   1331  CA  ASP   280       3.420  22.723  87.134  1.00 78.81
ATOM   1332  CB  ASP   280       2.171  22.387  87.972  1.00 78.81
ATOM   1333  CG  ASP   280       1.793  20.921  87.778  1.00 78.81
ATOM   1334  OD1 ASP   280       2.351  20.272  86.853  1.00 78.81
ATOM   1335  OD2 ASP   280       0.932  20.429  88.557  1.00 78.81
ATOM   1336  C   ASP   280       3.030  22.764  85.691  1.00 78.81
ATOM   1337  O   ASP   280       3.170  21.773  84.979  1.00 78.81
ATOM   1338  N   GLY   281       2.542  23.920  85.202  1.00 25.80
ATOM   1339  CA  GLY   281       2.096  23.971  83.838  1.00 25.80
ATOM   1340  C   GLY   281       3.249  23.655  82.943  1.00 25.80
ATOM   1341  O   GLY   281       3.109  22.929  81.960  1.00 25.80
ATOM   1342  N   PHE   282       4.428  24.220  83.251  1.00106.36
ATOM   1343  CA  PHE   282       5.584  23.975  82.445  1.00106.36
ATOM   1344  CB  PHE   282       6.742  24.933  82.760  1.00106.36
ATOM   1345  CG  PHE   282       6.193  26.279  82.417  1.00106.36
ATOM   1346  CD1 PHE   282       5.939  26.615  81.107  1.00106.36
ATOM   1347  CD2 PHE   282       5.873  27.191  83.396  1.00106.36
ATOM   1348  CE1 PHE   282       5.420  27.847  80.783  1.00106.36
ATOM   1349  CE2 PHE   282       5.354  28.426  83.081  1.00106.36
ATOM   1350  CZ  PHE   282       5.129  28.759  81.769  1.00106.36
ATOM   1351  C   PHE   282       5.994  22.546  82.609  1.00106.36
ATOM   1352  O   PHE   282       6.395  21.879  81.655  1.00106.36
ATOM   1353  N   ASN   283       5.894  22.022  83.837  1.00 71.40
ATOM   1354  CA  ASN   283       6.291  20.668  84.067  1.00 71.40
ATOM   1355  CB  ASN   283       6.129  20.284  85.548  1.00 71.40
ATOM   1356  CG  ASN   283       7.090  19.149  85.868  1.00 71.40
ATOM   1357  OD1 ASN   283       7.211  18.171  85.133  1.00 71.40
ATOM   1358  ND2 ASN   283       7.820  19.297  87.008  1.00 71.40
ATOM   1359  C   ASN   283       5.407  19.779  83.242  1.00 71.40
ATOM   1360  O   ASN   283       5.874  18.832  82.610  1.00 71.40
ATOM   1361  N   THR   284       4.096  20.080  83.210  1.00 44.86
ATOM   1362  CA  THR   284       3.160  19.258  82.495  1.00 44.86
ATOM   1363  CB  THR   284       1.723  19.648  82.719  1.00 44.86
ATOM   1364  OG1 THR   284       1.471  20.953  82.223  1.00 44.86
ATOM   1365  CG2 THR   284       1.431  19.587  84.228  1.00 44.86
ATOM   1366  C   THR   284       3.429  19.312  81.021  1.00 44.86
ATOM   1367  O   THR   284       3.338  18.295  80.336  1.00 44.86
ATOM   1368  N   ASN   285       3.767  20.490  80.464  1.00113.18
ATOM   1369  CA  ASN   285       3.937  20.471  79.040  1.00113.18
ATOM   1370  CB  ASN   285       4.035  21.849  78.339  1.00113.18
ATOM   1371  CG  ASN   285       5.264  22.649  78.742  1.00113.18
ATOM   1372  OD1 ASN   285       5.305  23.238  79.820  1.00113.18
ATOM   1373  ND2 ASN   285       6.279  22.708  77.839  1.00113.18
ATOM   1374  C   ASN   285       5.103  19.610  78.677  1.00113.18
ATOM   1375  O   ASN   285       5.067  18.915  77.663  1.00113.18
ATOM   1376  N   HIS   286       6.174  19.630  79.493  1.00 90.92
ATOM   1377  CA  HIS   286       7.325  18.828  79.199  1.00 90.92
ATOM   1378  ND1 HIS   286       8.719  21.730  80.154  1.00 90.92
ATOM   1379  CG  HIS   286       9.117  20.516  79.637  1.00 90.92
ATOM   1380  CB  HIS   286       8.553  19.186  80.056  1.00 90.92
ATOM   1381  NE2 HIS   286      10.242  22.175  78.595  1.00 90.92
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ATOM   1382  CD2 HIS   286      10.049  20.808  78.687  1.00 90.92
ATOM   1383  CE1 HIS   286       9.423  22.686  79.496  1.00 90.92
ATOM   1384  C   HIS   286       6.981  17.374  79.330  1.00 90.92
ATOM   1385  O   HIS   286       7.465  16.548  78.558  1.00 90.92
ATOM   1386  N   ARG   287       6.138  17.004  80.312  1.00141.18
ATOM   1387  CA  ARG   287       5.788  15.618  80.444  1.00141.18
ATOM   1388  CB  ARG   287       4.986  15.299  81.722  1.00141.18
ATOM   1389  CG  ARG   287       3.659  16.045  81.861  1.00141.18
ATOM   1390  CD  ARG   287       3.010  15.899  83.240  1.00141.18
ATOM   1391  NE  ARG   287       2.505  14.503  83.359  1.00141.18
ATOM   1392  CZ  ARG   287       2.130  14.010  84.576  1.00141.18
ATOM   1393  NH1 ARG   287       2.255  14.780  85.697  1.00141.18
ATOM   1394  NH2 ARG   287       1.628  12.745  84.674  1.00141.18
ATOM   1395  C   ARG   287       5.012  15.190  79.231  1.00141.18
ATOM   1396  O   ARG   287       5.196  14.084  78.724  1.00141.18
ATOM   1397  N   HIS   288       4.133  16.070  78.717  1.00 43.21
ATOM   1398  CA  HIS   288       3.338  15.721  77.574  1.00 43.21
ATOM   1399  ND1 HIS   288       1.012  17.652  79.158  1.00 43.21
ATOM   1400  CG  HIS   288       1.124  16.884  78.021  1.00 43.21
ATOM   1401  CB  HIS   288       2.343  16.816  77.150  1.00 43.21
ATOM   1402  NE2 HIS   288      -0.925  16.585  78.920  1.00 43.21
ATOM   1403  CD2 HIS   288      -0.068  16.239  77.890  1.00 43.21
ATOM   1404  CE1 HIS   288      -0.231  17.436  79.655  1.00 43.21
ATOM   1405  C   HIS   288       4.234  15.466  76.408  1.00 43.21
ATOM   1406  O   HIS   288       4.005  14.539  75.632  1.00 43.21
ATOM   1407  N   SER   289       5.288  16.283  76.253  1.00 89.65
ATOM   1408  CA  SER   289       6.140  16.122  75.117  1.00 89.65
ATOM   1409  CB  SER   289       7.274  17.163  75.059  1.00 89.65
ATOM   1410  OG  SER   289       8.195  16.969  76.123  1.00 89.65
ATOM   1411  C   SER   289       6.756  14.760  75.151  1.00 89.65
ATOM   1412  O   SER   289       6.803  14.067  74.135  1.00 89.65
ATOM   1413  N   VAL   290       7.217  14.320  76.336  1.00 99.64
ATOM   1414  CA  VAL   290       7.893  13.056  76.415  1.00 99.64
ATOM   1415  CB  VAL   290       8.469  12.758  77.774  1.00 99.64
ATOM   1416  CG1 VAL   290       7.346  12.382  78.758  1.00 99.64
ATOM   1417  CG2 VAL   290       9.536  11.666  77.605  1.00 99.64
ATOM   1418  C   VAL   290       6.953  11.956  76.037  1.00 99.64
ATOM   1419  O   VAL   290       7.327  11.026  75.320  1.00 99.64
ATOM   1420  N   LEU   291       5.691  12.036  76.497  1.00 46.15
ATOM   1421  CA  LEU   291       4.779  10.965  76.218  1.00 46.15
ATOM   1422  CB  LEU   291       3.395  11.206  76.843  1.00 46.15
ATOM   1423  CG  LEU   291       3.406  11.257  78.381  1.00 46.15
ATOM   1424  CD2 LEU   291       4.089  10.018  78.976  1.00 46.15
ATOM   1425  CD1 LEU   291       1.993  11.495  78.941  1.00 46.15
ATOM   1426  C   LEU   291       4.587  10.835  74.738  1.00 46.15
ATOM   1427  O   LEU   291       4.734   9.747  74.188  1.00 46.15
ATOM   1428  N   ASP   292       4.279  11.942  74.041  1.00 47.77
ATOM   1429  CA  ASP   292       4.022  11.838  72.632  1.00 47.77
ATOM   1430  CB  ASP   292       3.490  13.142  72.008  1.00 47.77
ATOM   1431  CG  ASP   292       2.051  13.321  72.471  1.00 47.77
ATOM   1432  OD1 ASP   292       1.653  12.617  73.437  1.00 47.77
ATOM   1433  OD2 ASP   292       1.328  14.153  71.860  1.00 47.77
ATOM   1434  C   ASP   292       5.268  11.458  71.892  1.00 47.77
ATOM   1435  O   ASP   292       5.248  10.591  71.021  1.00 47.77
ATOM   1436  N   ASN   293       6.401  12.074  72.258  1.00 70.18
ATOM   1437  CA  ASN   293       7.631  11.877  71.552  1.00 70.18
ATOM   1438  CB  ASN   293       8.800  12.681  72.147  1.00 70.18
ATOM   1439  CG  ASN   293       8.565  14.161  71.889  1.00 70.18
ATOM   1440  OD1 ASN   293       8.744  14.990  72.780  1.00 70.18
ATOM   1441  ND2 ASN   293       8.158  14.506  70.638  1.00 70.18
ATOM   1442  C   ASN   293       8.041  10.445  71.641  1.00 70.18
ATOM   1443  O   ASN   293       8.595   9.890  70.694  1.00 70.18
ATOM   1444  N   THR   294       7.720   9.801  72.774  1.00170.59
ATOM   1445  CA  THR   294       8.211   8.503  73.129  1.00170.59
ATOM   1446  CB  THR   294       7.949   8.123  74.555  1.00170.59
ATOM   1447  OG1 THR   294       8.805   7.051  74.907  1.00170.59
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ATOM	1448	CG2	THR	294	6.491	7.702	74.748	1.00170.59
ATOM	1449	C	THR	294	7.757	7.433	72.190	1.00170.59
ATOM	1450	O	THR	294	8.237	6.304	72.282	1.00170.59
ATOM	1451	N	ASN	295	6.774	7.731	71.317	1.00213.44
ATOM	1452	CA	ASN	295	6.301	6.773	70.350	1.00213.44
ATOM	1453	CB	ASN	295	5.514	7.401	69.190	1.00213.44
ATOM	1454	CG	ASN	295	5.078	6.279	68.254	1.00213.44
ATOM	1455	OD1	ASN	295	5.051	6.437	67.033	1.00213.44
ATOM	1456	ND2	ASN	295	4.729	5.109	68.851	1.00213.44
ATOM	1457	C	ASN	295	7.468	6.132	69.673	1.00213.44
ATOM	1458	O	ASN	295	8.429	6.801	69.292	1.00213.44
ATOM	1459	N	CYS	296	7.412	4.792	69.533	1.00101.49
ATOM	1460	CA	CYS	296	8.454	4.083	68.851	1.00101.49
ATOM	1461	CB	CYS	296	8.568	2.604	69.264	1.00101.49
ATOM	1462	SG	CYS	296	9.930	1.754	68.413	1.00101.49
ATOM	1463	C	CYS	296	8.104	4.134	67.402	1.00101.49
ATOM	1464	O	CYS	296	6.929	4.186	67.044	1.00101.49
ATOM	1465	N	ASP	297	9.119	4.140	66.521	1.00198.12
ATOM	1466	CA	ASP	297	8.815	4.244	65.127	1.00198.12
ATOM	1467	CB	ASP	297	10.019	4.633	64.246	1.00198.12
ATOM	1468	CG	ASP	297	11.101	3.567	64.361	1.00198.12
ATOM	1469	OD1	ASP	297	11.108	2.835	65.387	1.00198.12
ATOM	1470	OD2	ASP	297	11.935	3.473	63.422	1.00198.12
ATOM	1471	C	ASP	297	8.269	2.946	64.633	1.00198.12
ATOM	1472	O	ASP	297	8.807	1.874	64.906	1.00198.12
ATOM	1473	N	ILE	298	7.142	3.027	63.905	1.00116.45
ATOM	1474	CA	ILE	298	6.549	1.879	63.287	1.00116.45
ATOM	1475	CB	ILE	298	5.264	1.433	63.922	1.00116.45
ATOM	1476	CG2	ILE	298	4.663	0.329	63.035	1.00116.45
ATOM	1477	CG1	ILE	298	5.513	0.971	65.367	1.00116.45
ATOM	1478	CD1	ILE	298	6.452	-0.232	65.460	1.00116.45
ATOM	1479	C	ILE	298	6.254	2.310	61.889	1.00116.45
ATOM	1480	O	ILE	298	5.966	3.481	61.648	1.00116.45
ATOM	1481	N	ASP	299	6.333	1.387	60.914	1.00128.04
ATOM	1482	CA	ASP	299	6.120	1.839	59.573	1.00128.04
ATOM	1483	CB	ASP	299	6.821	0.987	58.505	1.00128.04
ATOM	1484	CG	ASP	299	8.305	1.313	58.560	1.00128.04
ATOM	1485	OD1	ASP	299	8.641	2.446	58.996	1.00128.04
ATOM	1486	OD2	ASP	299	9.123	0.440	58.162	1.00128.04
ATOM	1487	C	ASP	299	4.663	1.841	59.266	1.00128.04
ATOM	1488	O	ASP	299	4.075	0.803	58.966	1.00128.04
ATOM	1489	N	VAL	300	4.045	3.036	59.358	1.00 95.52
ATOM	1490	CA	VAL	300	2.676	3.219	58.980	1.00 95.52
ATOM	1491	CB	VAL	300	1.693	3.088	60.109	1.00 95.52
ATOM	1492	CG1	VAL	300	1.938	4.223	61.112	1.00 95.52
ATOM	1493	CG2	VAL	300	0.271	3.068	59.522	1.00 95.52
ATOM	1494	C	VAL	300	2.586	4.610	58.444	1.00 95.52
ATOM	1495	O	VAL	300	3.372	5.482	58.813	1.00 95.52
ATOM	1496	N	LEU	301	1.639	4.850	57.521	1.00134.46
ATOM	1497	CA	LEU	301	1.513	6.160	56.958	1.00134.46
ATOM	1498	CB	LEU	301	0.478	6.198	55.812	1.00134.46
ATOM	1499	CG	LEU	301	0.286	7.570	55.135	1.00134.46
ATOM	1500	CD2	LEU	301	1.623	8.122	54.624	1.00134.46
ATOM	1501	CD1	LEU	301	-0.477	8.575	56.022	1.00134.46
ATOM	1502	C	LEU	301	1.070	7.096	58.034	1.00134.46
ATOM	1503	O	LEU	301	1.647	8.167	58.210	1.00134.46
ATOM	1504	N	PHE	302	0.051	6.683	58.809	1.00199.62
ATOM	1505	CA	PHE	302	-0.511	7.566	59.788	1.00199.62
ATOM	1506	CB	PHE	302	-1.706	6.990	60.564	1.00199.62
ATOM	1507	CG	PHE	302	-2.899	7.050	59.679	1.00199.62
ATOM	1508	CD1	PHE	302	-3.141	6.069	58.746	1.00199.62
ATOM	1509	CD2	PHE	302	-3.783	8.099	59.792	1.00199.62
ATOM	1510	CE1	PHE	302	-4.251	6.139	57.938	1.00199.62
ATOM	1511	CE2	PHE	302	-4.894	8.174	58.987	1.00199.62
ATOM	1512	CZ	PHE	302	-5.128	7.192	58.057	1.00199.62
ATOM	1513	C	PHE	302	0.527	7.940	60.779	1.00199.62

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ATOM   1514  O   PHE   302       1.359   7.129  61.181  1.00199.62
ATOM   1515  N   ARG   303       0.492   9.225  61.173  1.00292.70
ATOM   1516  CA  ARG   303       1.403   9.730  62.147  1.00292.70
ATOM   1517  CB  ARG   303       1.470  11.268  62.135  1.00292.70
ATOM   1518  CG  ARG   303       1.638  11.837  60.722  1.00292.70
ATOM   1519  CD  ARG   303       2.555  11.002  59.823  1.00292.70
ATOM   1520  NE  ARG   303       3.962  11.304  60.204  1.00292.70
ATOM   1521  CZ  ARG   303       4.645  12.265  59.519  1.00292.70
ATOM   1522  NH1 ARG   303       4.042  12.911  58.477  1.00292.70
ATOM   1523  NH2 ARG   303       5.926  12.578  59.870  1.00292.70
ATOM   1524  C   ARG   303       0.840   9.292  63.457  1.00292.70
ATOM   1525  O   ARG   303      -0.374   9.323  63.656  1.00292.70
ATOM   1526  N   PHE   304       1.696   8.828  64.386  1.00364.50
ATOM   1527  CA  PHE   304       1.136   8.409  65.635  1.00364.50
ATOM   1528  CB  PHE   304       0.619   6.960  65.616  1.00364.50
ATOM   1529  CG  PHE   304       1.788   6.043  65.500  1.00364.50
ATOM   1530  CD1 PHE   304       2.484   5.926  64.319  1.00364.50
ATOM   1531  CD2 PHE   304       2.179   5.282  66.579  1.00364.50
ATOM   1532  CE1 PHE   304       3.561   5.076  64.219  1.00364.50
ATOM   1533  CE2 PHE   304       3.252   4.430  66.486  1.00364.50
ATOM   1534  CZ  PHE   304       3.948   4.329  65.305  1.00364.50
ATOM   1535  C   PHE   304       2.211   8.484  66.662  1.00364.50
ATOM   1536  O   PHE   304       3.395   8.553  66.337  1.00364.50
ATOM   1537  N   PHE   305       1.813   8.500  67.948  1.00306.52
ATOM   1538  CA  PHE   305       2.791   8.519  68.989  1.00306.52
ATOM   1539  CB  PHE   305       2.949   9.878  69.683  1.00306.52
ATOM   1540  CG  PHE   305       3.405  10.843  68.644  1.00306.52
ATOM   1541  CD1 PHE   305       4.742  10.999  68.357  1.00306.52
ATOM   1542  CD2 PHE   305       2.483  11.584  67.941  1.00306.52
ATOM   1543  CE1 PHE   305       5.151  11.892  67.394  1.00306.52
ATOM   1544  CE2 PHE   305       2.884  12.476  66.980  1.00306.52
ATOM   1545  CZ  PHE   305       4.222  12.633  66.704  1.00306.52
ATOM   1546  C   PHE   305       2.345   7.530  70.011  1.00306.52
ATOM   1547  O   PHE   305       1.177   7.147  70.053  1.00306.52
ATOM   1548  N   GLU   306       3.284   7.068  70.857  1.00342.97
ATOM   1549  CA  GLU   306       2.943   6.091  71.839  1.00342.97
ATOM   1550  CB  GLU   306       3.653   4.743  71.637  1.00342.97
ATOM   1551  CG  GLU   306       3.154   3.659  72.591  1.00342.97
ATOM   1552  CD  GLU   306       1.759   3.263  72.136  1.00342.97
ATOM   1553  OE1 GLU   306       0.911   4.177  71.957  1.00342.97
ATOM   1554  OE2 GLU   306       1.526   2.040  71.953  1.00342.97
ATOM   1555  C   GLU   306       3.403   6.632  73.134  1.00342.97
ATOM   1556  O   GLU   306       4.288   7.477  73.156  1.00342.97
ATOM   1557  N   CYS   307       2.782   6.194  74.242  1.00213.88
ATOM   1558  CA  CYS   307       3.216   6.642  75.528  1.00213.88
ATOM   1559  CB  CYS   307       2.049   6.937  76.485  1.00213.88
ATOM   1560  SG  CYS   307       2.584   7.483  78.133  1.00213.88
ATOM   1561  C   CYS   307       3.980   5.518  76.139  1.00213.88
ATOM   1562  O   CYS   307       3.536   4.924  77.120  1.00213.88
ATOM   1563  N   THR   308       5.153   5.179  75.571  1.00 57.58
ATOM   1564  CA  THR   308       5.880   4.113  76.186  1.00 57.58
ATOM   1565  CB  THR   308       7.029   3.587  75.371  1.00 57.58
ATOM   1566  OG1 THR   308       8.022   4.581  75.190  1.00 57.58
ATOM   1567  CG2 THR   308       6.482   3.124  74.008  1.00 57.58
ATOM   1568  C   THR   308       6.367   4.607  77.510  1.00 57.58
ATOM   1569  O   THR   308       6.287   3.892  78.508  1.00 57.58
ATOM   1570  N   PHE   309       6.869   5.859  77.568  1.00 67.82
ATOM   1571  CA  PHE   309       7.312   6.349  78.840  1.00 67.82
ATOM   1572  CB  PHE   309       8.826   6.214  79.115  1.00 67.82
ATOM   1573  CG  PHE   309       9.636   6.893  78.063  1.00 67.82
ATOM   1574  CD1 PHE   309       9.635   8.263  77.934  1.00 67.82
ATOM   1575  CD2 PHE   309      10.439   6.147  77.228  1.00 67.82
ATOM   1576  CE1 PHE   309      10.399   8.871  76.964  1.00 67.82
ATOM   1577  CE2 PHE   309      11.207   6.748  76.258  1.00 67.82
ATOM   1578  CZ  PHE   309      11.184   8.116  76.125  1.00 67.82
ATOM   1579  C   PHE   309       6.919   7.779  79.026  1.00 67.82
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ATOM   1580  O   PHE   309       6.449   8.450  78.106  1.00 67.82
ATOM   1581  N   GLY   310       7.095   8.266  80.272  1.00 35.84
ATOM   1582  CA  GLY   310       6.795   9.622  80.629  1.00 35.84
ATOM   1583  C   GLY   310       5.596   9.675  81.529  1.00 35.84
ATOM   1584  O   GLY   310       5.433  10.622  82.292  1.00 35.84
ATOM   1585  N   ALA   311       4.715   8.665  81.494  1.00 33.99
ATOM   1586  CA  ALA   311       3.551   8.737  82.334  1.00 33.99
ATOM   1587  CB  ALA   311       2.593   7.553  82.123  1.00 33.99
ATOM   1588  C   ALA   311       3.963   8.717  83.777  1.00 33.99
ATOM   1589  O   ALA   311       3.420   9.452  84.601  1.00 33.99
ATOM   1590  N   LYS   312       4.942   7.855  84.105  1.00 97.86
ATOM   1591  CA  LYS   312       5.431   7.608  85.435  1.00 97.86
ATOM   1592  CB  LYS   312       6.471   6.478  85.476  1.00 97.86
ATOM   1593  CG  LYS   312       7.054   6.237  86.870  1.00 97.86
ATOM   1594  CD  LYS   312       8.056   5.083  86.912  1.00 97.86
ATOM   1595  CE  LYS   312       8.821   4.978  88.232  1.00 97.86
ATOM   1596  NZ  LYS   312       9.860   3.929  88.129  1.00 97.86
ATOM   1597  C   LYS   312       6.119   8.801  86.022  1.00 97.86
ATOM   1598  O   LYS   312       6.024   9.029  87.226  1.00 97.86
ATOM   1599  N   ILE   313       6.830   9.577  85.180  1.00184.69
ATOM   1600  CA  ILE   313       7.702  10.644  85.599  1.00184.69
ATOM   1601  CB  ILE   313       8.110  11.557  84.467  1.00184.69
ATOM   1602  CG2 ILE   313       6.838  12.252  83.963  1.00184.69
ATOM   1603  CG1 ILE   313       9.144  12.612  84.889  1.00184.69
ATOM   1604  CD1 ILE   313       8.499  13.804  85.601  1.00184.69
ATOM   1605  C   ILE   313       7.132  11.465  86.706  1.00184.69
ATOM   1606  O   ILE   313       5.961  11.845  86.706  1.00184.69
ATOM   1607  N   GLY   314       7.997  11.749  87.704  1.00 35.77
ATOM   1608  CA  GLY   314       7.623  12.563  88.821  1.00 35.77
ATOM   1609  C   GLY   314       8.114  13.944  88.534  1.00 35.77
ATOM   1610  O   GLY   314       9.280  14.149  88.197  1.00 35.77
ATOM   1611  N   CYS   315       7.215  14.934  88.701  1.00 51.27
ATOM   1612  CA  CYS   315       7.513  16.300  88.388  1.00 51.27
ATOM   1613  CB  CYS   315       6.266  17.071  87.920  1.00 51.27
ATOM   1614  SG  CYS   315       5.480  16.313  86.465  1.00 51.27
ATOM   1615  C   CYS   315       7.996  16.961  89.641  1.00 51.27
ATOM   1616  O   CYS   315       7.345  16.879  90.680  1.00 51.27
ATOM   1617  N   ILE   316       9.167  17.633  89.588  1.00113.12
ATOM   1618  CA  ILE   316       9.648  18.251  90.791  1.00113.12
ATOM   1619  CB  ILE   316      10.793  17.532  91.440  1.00113.12
ATOM   1620  CG2 ILE   316      10.331  16.122  91.832  1.00113.12
ATOM   1621  CG1 ILE   316      12.019  17.553  90.513  1.00113.12
ATOM   1622  CD1 ILE   316      13.308  17.116  91.205  1.00113.12
ATOM   1623  C   ILE   316      10.183  19.612  90.486  1.00113.12
ATOM   1624  O   ILE   316      10.554  19.915  89.352  1.00113.12
ATOM   1625  N   ASN   317      10.206  20.482  91.518  1.00 92.47
ATOM   1626  CA  ASN   317      10.838  21.761  91.377  1.00 92.47
ATOM   1627  CB  ASN   317      10.161  22.905  92.150  1.00 92.47
ATOM   1628  CG  ASN   317      10.876  24.189  91.747  1.00 92.47
ATOM   1629  OD1 ASN   317      10.384  24.950  90.915  1.00 92.47
ATOM   1630  ND2 ASN   317      12.075  24.434  92.341  1.00 92.47
ATOM   1631  C   ASN   317      12.201  21.563  91.963  1.00 92.47
ATOM   1632  O   ASN   317      12.334  21.185  93.126  1.00 92.47
ATOM   1633  N   VAL   318      13.250  21.804  91.152  1.00256.82
ATOM   1634  CA  VAL   318      14.596  21.482  91.537  1.00256.82
ATOM   1635  CB  VAL   318      15.623  21.610  90.449  1.00256.82
ATOM   1636  CG1 VAL   318      15.173  20.771  89.246  1.00256.82
ATOM   1637  CG2 VAL   318      15.914  23.088  90.171  1.00256.82
ATOM   1638  C   VAL   318      15.119  22.296  92.674  1.00256.82
ATOM   1639  O   VAL   318      15.781  21.736  93.533  1.00256.82
ATOM   1640  N   GLU   319      14.886  23.621  92.735  1.00148.90
ATOM   1641  CA  GLU   319      15.486  24.392  93.794  1.00148.90
ATOM   1642  CB  GLU   319      15.190  23.832  95.199  1.00148.90
ATOM   1643  CG  GLU   319      13.709  23.927  95.574  1.00148.90
ATOM   1644  CD  GLU   319      13.460  23.130  96.851  1.00148.90
ATOM   1645  OE1 GLU   319      13.574  21.877  96.798  1.00148.90
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ATOM   1646  OE2 GLU   319      13.148  23.765  97.892  1.00148.90
ATOM   1647  C   GLU   319      16.978  24.456  93.572  1.00148.90
ATOM   1648  O   GLU   319      17.639  23.445  93.335  1.00148.90
ATOM   1649  N   VAL   320      17.541  25.684  93.630  1.00135.20
ATOM   1650  CA  VAL   320      18.939  25.956  93.415  1.00135.20
ATOM   1651  CB  VAL   320      19.301  26.059  91.973  1.00135.20
ATOM   1652  CG1 VAL   320      19.047  24.688  91.331  1.00135.20
ATOM   1653  CG2 VAL   320      18.490  27.217  91.365  1.00135.20
ATOM   1654  C   VAL   320      19.198  27.310  94.009  1.00135.20
ATOM   1655  O   VAL   320      18.335  27.853  94.695  1.00135.20
ATOM   1656  N   ASN   321      20.400  27.891  93.786  1.00 93.84
ATOM   1657  CA  ASN   321      20.666  29.190  94.359  1.00 93.84
ATOM   1658  CB  ASN   321      21.812  29.200  95.388  1.00 93.84
ATOM   1659  CG  ASN   321      21.303  28.624  96.706  1.00 93.84
ATOM   1660  OD1 ASN   321      20.829  27.491  96.775  1.00 93.84
ATOM   1661  ND2 ASN   321      21.410  29.436  97.792  1.00 93.84
ATOM   1662  C   ASN   321      21.035  30.190  93.295  1.00 93.84
ATOM   1663  O   ASN   321      21.555  29.809  92.247  1.00 93.84
ATOM   1664  N   GLN   322      20.714  31.494  93.532  1.00148.83
ATOM   1665  CA  GLN   322      21.092  32.602  92.679  1.00148.83
ATOM   1666  CB  GLN   322      20.070  32.903  91.568  1.00148.83
ATOM   1667  CG  GLN   322      20.478  34.077  90.674  1.00148.83
ATOM   1668  CD  GLN   322      19.349  34.341  89.685  1.00148.83
ATOM   1669  OE1 GLN   322      18.191  34.027  89.953  1.00148.83
ATOM   1670  NE2 GLN   322      19.687  34.933  88.508  1.00148.83
ATOM   1671  C   GLN   322      21.136  33.844  93.533  1.00148.83
ATOM   1672  O   GLN   322      20.094  34.357  93.940  1.00148.83
ATOM   1673  N   LEU   323      22.347  34.356  93.837  1.00 98.47
ATOM   1674  CA  LEU   323      22.494  35.530  94.658  1.00 98.47
ATOM   1675  CB  LEU   323      23.936  35.739  95.155  1.00 98.47
ATOM   1676  CG  LEU   323      24.402  34.643  96.134  1.00 98.47
ATOM   1677  CD2 LEU   323      25.708  35.041  96.839  1.00 98.47
ATOM   1678  CD1 LEU   323      24.481  33.271  95.446  1.00 98.47
ATOM   1679  C   LEU   323      22.063  36.788  93.956  1.00 98.47
ATOM   1680  O   LEU   323      21.361  37.611  94.542  1.00 98.47
ATOM   1681  N   LEU   324      22.461  36.971  92.679  1.00102.11
ATOM   1682  CA  LEU   324      22.197  38.215  91.998  1.00102.11
ATOM   1683  CB  LEU   324      23.396  38.736  91.189  1.00102.11
ATOM   1684  CG  LEU   324      24.622  39.078  92.054  1.00102.11
ATOM   1685  CD2 LEU   324      25.679  39.847  91.245  1.00102.11
ATOM   1686  CD1 LEU   324      25.189  37.824  92.735  1.00102.11
ATOM   1687  C   LEU   324      21.072  38.030  91.029  1.00102.11
ATOM   1688  O   LEU   324      20.724  36.910  90.663  1.00102.11
ATOM   1689  N   GLU   325      20.431  39.156  90.650  1.00108.72
ATOM   1690  CA  GLU   325      19.301  39.181  89.763  1.00108.72
ATOM   1691  CB  GLU   325      18.537  40.512  89.835  1.00108.72
ATOM   1692  CG  GLU   325      17.134  40.441  89.235  1.00108.72
ATOM   1693  CD  GLU   325      16.380  41.683  89.684  1.00108.72
ATOM   1694  OE1 GLU   325      17.036  42.746  89.850  1.00108.72
ATOM   1695  OE2 GLU   325      15.137  41.585  89.868  1.00108.72
ATOM   1696  C   GLU   325      19.644  38.919  88.314  1.00108.72
ATOM   1697  O   GLU   325      18.895  38.230  87.627  1.00108.72
ATOM   1698  N   SER   326      20.757  39.493  87.804  1.00114.97
ATOM   1699  CA  SER   326      21.134  39.467  86.406  1.00114.97
ATOM   1700  CB  SER   326      22.097  40.613  86.069  1.00114.97
ATOM   1701  OG  SER   326      21.438  41.862  86.241  1.00114.97
ATOM   1702  C   SER   326      21.748  38.170  85.936  1.00114.97
ATOM   1703  O   SER   326      21.853  37.921  84.736  1.00114.97
ATOM   1704  N   GLU   327      22.181  37.316  86.870  1.00104.93
ATOM   1705  CA  GLU   327      22.890  36.083  86.653  1.00104.93
ATOM   1706  CB  GLU   327      23.539  35.575  87.950  1.00104.93
ATOM   1707  CG  GLU   327      24.691  36.466  88.432  1.00104.93
ATOM   1708  CD  GLU   327      25.159  35.965  89.792  1.00104.93
ATOM   1709  OE1 GLU   327      24.287  35.748  90.677  1.00104.93
ATOM   1710  OE2 GLU   327      26.396  35.797  89.967  1.00104.93
ATOM   1711  C   GLU   327      22.049  34.976  86.057  1.00104.93
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ATOM	1712	O	GLU	327	22.597	33.944	85.674	1.00104.93
ATOM	1713	N	CYS	328	20.712	35.125	85.963	1.00 88.66
ATOM	1714	CA	CYS	328	19.835	34.019	85.648	1.00 88.66
ATOM	1715	CB	CYS	328	18.367	34.439	85.426	1.00 88.66
ATOM	1716	SG	CYS	328	18.128	35.433	83.921	1.00 88.66
ATOM	1717	C	CYS	328	20.255	33.241	84.426	1.00 88.66
ATOM	1718	O	CYS	328	20.216	32.013	84.459	1.00 88.66
ATOM	1719	N	GLY	329	20.650	33.889	83.316	1.00 48.60
ATOM	1720	CA	GLY	329	21.026	33.129	82.149	1.00 48.60
ATOM	1721	C	GLY	329	22.236	32.301	82.465	1.00 48.60
ATOM	1722	O	GLY	329	22.398	31.182	81.981	1.00 48.60
ATOM	1723	N	MET	330	23.148	32.862	83.269	1.00133.02
ATOM	1724	CA	MET	330	24.370	32.223	83.650	1.00133.02
ATOM	1725	CB	MET	330	25.183	33.184	84.533	1.00133.02
ATOM	1726	CG	MET	330	26.681	32.964	84.459	1.00133.02
ATOM	1727	SD	MET	330	27.124	31.237	84.706	1.00133.02
ATOM	1728	CE	MET	330	26.458	31.100	86.390	1.00133.02
ATOM	1729	C	MET	330	24.027	30.990	84.449	1.00133.02
ATOM	1730	O	MET	330	24.615	29.924	84.265	1.00133.02
ATOM	1731	N	PHE	331	23.036	31.109	85.354	1.00 83.63
ATOM	1732	CA	PHE	331	22.607	30.029	86.201	1.00 83.63
ATOM	1733	CB	PHE	331	21.599	30.466	87.280	1.00 83.63
ATOM	1734	CG	PHE	331	22.375	31.106	88.383	1.00 83.63
ATOM	1735	CD1	PHE	331	22.824	32.400	88.281	1.00 83.63
ATOM	1736	CD2	PHE	331	22.650	30.399	89.530	1.00 83.63
ATOM	1737	CE1	PHE	331	23.538	32.971	89.311	1.00 83.63
ATOM	1738	CE2	PHE	331	23.366	30.972	90.557	1.00 83.63
ATOM	1739	CZ	PHE	331	23.812	32.262	90.451	1.00 83.63
ATOM	1740	C	PHE	331	21.992	28.937	85.379	1.00 83.63
ATOM	1741	O	PHE	331	22.178	27.760	85.688	1.00 83.63
ATOM	1742	N	ILE	332	21.228	29.279	84.319	1.00106.83
ATOM	1743	CA	ILE	332	20.640	28.222	83.545	1.00106.83
ATOM	1744	CB	ILE	332	19.753	28.643	82.400	1.00106.83
ATOM	1745	CG2	ILE	332	18.631	29.519	82.984	1.00106.83
ATOM	1746	CG1	ILE	332	20.539	29.315	81.268	1.00106.83
ATOM	1747	CD1	ILE	332	19.748	29.434	79.964	1.00106.83
ATOM	1748	C	ILE	332	21.772	27.428	82.972	1.00106.83
ATOM	1749	O	ILE	332	21.715	26.202	82.906	1.00106.83
ATOM	1750	N	SER	333	22.837	28.125	82.537	1.00 51.79
ATOM	1751	CA	SER	333	24.000	27.510	81.960	1.00 51.79
ATOM	1752	CB	SER	333	25.082	28.555	81.640	1.00 51.79
ATOM	1753	OG	SER	333	24.618	29.446	80.638	1.00 51.79
ATOM	1754	C	SER	333	24.613	26.548	82.947	1.00 51.79
ATOM	1755	O	SER	333	24.893	25.402	82.597	1.00 51.79
ATOM	1756	N	LEU	334	24.843	26.981	84.206	1.00121.38
ATOM	1757	CA	LEU	334	25.440	26.123	85.202	1.00121.38
ATOM	1758	CB	LEU	334	25.762	26.813	86.544	1.00121.38
ATOM	1759	CG	LEU	334	27.176	27.413	86.586	1.00121.38
ATOM	1760	CD2	LEU	334	27.429	28.161	87.905	1.00121.38
ATOM	1761	CD1	LEU	334	27.448	28.271	85.352	1.00121.38
ATOM	1762	C	LEU	334	24.542	24.973	85.501	1.00121.38
ATOM	1763	O	LEU	334	25.001	23.850	85.696	1.00121.38
ATOM	1764	N	PHE	335	23.230	25.226	85.556	1.00159.54
ATOM	1765	CA	PHE	335	22.292	24.196	85.851	1.00159.54
ATOM	1766	CB	PHE	335	20.865	24.767	85.906	1.00159.54
ATOM	1767	CG	PHE	335	19.899	23.684	86.217	1.00159.54
ATOM	1768	CD1	PHE	335	19.906	23.083	87.455	1.00159.54
ATOM	1769	CD2	PHE	335	18.970	23.298	85.280	1.00159.54
ATOM	1770	CE1	PHE	335	19.005	22.091	87.753	1.00159.54
ATOM	1771	CE2	PHE	335	18.069	22.306	85.573	1.00159.54
ATOM	1772	CZ	PHE	335	18.085	21.704	86.810	1.00159.54
ATOM	1773	C	PHE	335	22.388	23.163	84.775	1.00159.54
ATOM	1774	O	PHE	335	22.380	21.967	85.054	1.00159.54
ATOM	1775	N	MET	336	22.458	23.588	83.503	1.00155.16
ATOM	1776	CA	MET	336	22.560	22.615	82.458	1.00155.16
ATOM	1777	CB	MET	336	22.361	23.188	81.042	1.00155.16

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ATOM   1778  CG  MET   336      23.323  24.301  80.633  1.00155.16
ATOM   1779  SD  MET   336      23.119  24.827  78.905  1.00155.16
ATOM   1780  CE  MET   336      24.318  23.631  78.251  1.00155.16
ATOM   1781  C   MET   336      23.876  21.912  82.535  1.00155.16
ATOM   1782  O   MET   336      23.932  20.692  82.421  1.00155.16
ATOM   1783  N   ILE   337      24.979  22.643  82.775  1.00107.96
ATOM   1784  CA  ILE   337      26.257  21.998  82.747  1.00107.96
ATOM   1785  CB  ILE   337      27.408  22.968  82.889  1.00107.96
ATOM   1786  CG2 ILE   337      27.325  23.676  84.251  1.00107.96
ATOM   1787  CG1 ILE   337      28.745  22.255  82.635  1.00107.96
ATOM   1788  CD1 ILE   337      29.919  23.221  82.483  1.00107.96
ATOM   1789  C   ILE   337      26.349  20.969  83.830  1.00107.96
ATOM   1790  O   ILE   337      26.711  19.823  83.563  1.00107.96
ATOM   1791  N   LEU   338      26.009  21.320  85.084  1.00143.54
ATOM   1792  CA  LEU   338      26.178  20.325  86.096  1.00143.54
ATOM   1793  CB  LEU   338      26.128  20.815  87.546  1.00143.54
ATOM   1794  CG  LEU   338      24.723  20.956  88.125  1.00143.54
ATOM   1795  CD2 LEU   338      23.877  21.963  87.343  1.00143.54
ATOM   1796  CD1 LEU   338      24.834  21.309  89.605  1.00143.54
ATOM   1797  C   LEU   338      25.176  19.233  85.930  1.00143.54
ATOM   1798  O   LEU   338      25.494  18.064  86.118  1.00143.54
ATOM   1799  N   CYS   339      23.931  19.564  85.556  1.00 53.20
ATOM   1800  CA  CYS   339      22.950  18.526  85.471  1.00 53.20
ATOM   1801  CB  CYS   339      21.552  19.054  85.129  1.00 53.20
ATOM   1802  SG  CYS   339      20.905  20.013  86.534  1.00 53.20
ATOM   1803  C   CYS   339      23.383  17.513  84.458  1.00 53.20
ATOM   1804  O   CYS   339      23.210  16.313  84.665  1.00 53.20
ATOM   1805  N   THR   340      23.978  17.961  83.338  1.00 59.69
ATOM   1806  CA  THR   340      24.410  17.037  82.331  1.00 59.69
ATOM   1807  CB  THR   340      24.867  17.743  81.102  1.00 59.69
ATOM   1808  OG1 THR   340      26.007  18.545  81.373  1.00 59.69
ATOM   1809  CG2 THR   340      23.682  18.627  80.673  1.00 59.69
ATOM   1810  C   THR   340      25.503  16.173  82.890  1.00 59.69
ATOM   1811  O   THR   340      25.566  14.979  82.607  1.00 59.69
ATOM   1812  N   ARG   341      26.400  16.767  83.697  1.00166.50
ATOM   1813  CA  ARG   341      27.485  16.067  84.324  1.00166.50
ATOM   1814  CB  ARG   341      28.540  16.994  84.956  1.00166.50
ATOM   1815  CG  ARG   341      29.402  17.720  83.917  1.00166.50
ATOM   1816  CD  ARG   341      30.426  16.817  83.216  1.00166.50
ATOM   1817  NE  ARG   341      29.666  15.747  82.509  1.00166.50
ATOM   1818  CZ  ARG   341      30.255  14.997  81.531  1.00166.50
ATOM   1819  NH1 ARG   341      31.532  15.268  81.142  1.00166.50
ATOM   1820  NH2 ARG   341      29.559  13.977  80.950  1.00166.50
ATOM   1821  C   ARG   341      26.969  15.144  85.384  1.00166.50
ATOM   1822  O   ARG   341      27.625  14.155  85.703  1.00166.50
ATOM   1823  N   THR   342      25.773  15.453  85.929  1.00243.88
ATOM   1824  CA  THR   342      25.109  14.842  87.056  1.00243.88
ATOM   1825  CB  THR   342      25.115  13.329  87.094  1.00243.88
ATOM   1826  OG1 THR   342      26.378  12.820  87.496  1.00243.88
ATOM   1827  CG2 THR   342      24.757  12.802  85.693  1.00243.88
ATOM   1828  C   THR   342      25.625  15.308  88.408  1.00243.88
ATOM   1829  O   THR   342      25.437  14.562  89.369  1.00243.88
ATOM   1830  N   PRO   343      26.237  16.465  88.607  1.00235.84
ATOM   1831  CA  PRO   343      26.455  16.863  89.969  1.00235.84
ATOM   1832  CD  PRO   343      27.394  16.878  87.814  1.00235.84
ATOM   1833  CB  PRO   343      27.440  18.025  89.938  1.00235.84
ATOM   1834  CG  PRO   343      28.320  17.688  88.732  1.00235.84
ATOM   1835  C   PRO   343      25.199  17.159  90.732  1.00235.84
ATOM   1836  O   PRO   343      25.343  17.430  91.916  1.00235.84
ATOM   1837  N   PRO   344      24.013  17.210  90.200  1.00146.86
ATOM   1838  CA  PRO   344      22.908  17.373  91.105  1.00146.86
ATOM   1839  CD  PRO   344      23.778  17.891  88.936  1.00146.86
ATOM   1840  CB  PRO   344      21.731  17.831  90.252  1.00146.86
ATOM   1841  CG  PRO   344      22.405  18.572  89.085  1.00146.86
ATOM   1842  C   PRO   344      22.725  16.036  91.726  1.00146.86
ATOM   1843  O   PRO   344      23.180  15.072  91.117  1.00146.86
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ATOM	1844	N	LYS	345	22.109	15.944	92.923	1.00269.51
ATOM	1845	CA	LYS	345	21.937	14.657	93.535	1.00269.51
ATOM	1846	CB	LYS	345	22.991	14.317	94.601	1.00269.51
ATOM	1847	CG	LYS	345	24.410	14.175	94.054	1.00269.51
ATOM	1848	CD	LYS	345	24.559	13.061	93.019	1.00269.51
ATOM	1849	CE	LYS	345	25.977	12.940	92.455	1.00269.51
ATOM	1850	NZ	LYS	345	26.850	12.229	93.416	1.00269.51
ATOM	1851	C	LYS	345	20.637	14.655	94.265	1.00269.51
ATOM	1852	O	LYS	345	19.963	15.678	94.376	1.00269.51
ATOM	1853	N	SER	346	20.247	13.468	94.770	1.00 69.56
ATOM	1854	CA	SER	346	19.058	13.362	95.555	1.00 69.56
ATOM	1855	CB	SER	346	18.802	11.932	96.066	1.00 69.56
ATOM	1856	OG	SER	346	19.821	11.548	96.979	1.00 69.56
ATOM	1857	C	SER	346	19.293	14.225	96.748	1.00 69.56
ATOM	1858	O	SER	346	18.432	15.003	97.153	1.00 69.56
ATOM	1859	N	PHE	347	20.502	14.110	97.330	1.00222.83
ATOM	1860	CA	PHE	347	20.861	14.913	98.458	1.00222.83
ATOM	1861	CB	PHE	347	21.482	14.125	99.626	1.00222.83
ATOM	1862	CG	PHE	347	20.372	13.414	100.316	1.00222.83
ATOM	1863	CD1	PHE	347	19.858	12.247	99.804	1.00222.83
ATOM	1864	CD2	PHE	347	19.843	13.923	101.481	1.00222.83
ATOM	1865	CE1	PHE	347	18.831	11.598	100.447	1.00222.83
ATOM	1866	CE2	PHE	347	18.816	13.278	102.129	1.00222.83
ATOM	1867	CZ	PHE	347	18.308	12.113	101.609	1.00222.83
ATOM	1868	C	PHE	347	21.879	15.884	97.977	1.00222.83
ATOM	1869	O	PHE	347	22.550	15.648	96.974	1.00222.83
ATOM	1870	N	LYS	348	21.990	17.027	98.681	1.00288.70
ATOM	1871	CA	LYS	348	22.925	18.038	98.299	1.00288.70
ATOM	1872	CB	LYS	348	24.321	17.471	97.993	1.00288.70
ATOM	1873	CG	LYS	348	24.934	16.735	99.186	1.00288.70
ATOM	1874	CD	LYS	348	26.080	15.801	98.798	1.00288.70
ATOM	1875	CE	LYS	348	25.601	14.449	98.265	1.00288.70
ATOM	1876	NZ	LYS	348	26.768	13.593	97.958	1.00288.70
ATOM	1877	C	LYS	348	22.379	18.685	97.068	1.00288.70
ATOM	1878	O	LYS	348	21.881	18.011	96.168	1.00288.70
ATOM	1879	N	SER	349	22.438	20.031	97.016	1.00159.92
ATOM	1880	CA	SER	349	21.932	20.754	95.887	1.00159.92
ATOM	1881	CB	SER	349	21.494	22.193	96.215	1.00159.92
ATOM	1882	OG	SER	349	20.391	22.176	97.112	1.00159.92
ATOM	1883	C	SER	349	23.021	20.837	94.878	1.00159.92
ATOM	1884	O	SER	349	24.086	20.248	95.051	1.00159.92
ATOM	1885	N	LEU	350	22.767	21.569	93.776	1.00150.01
ATOM	1886	CA	LEU	350	23.746	21.711	92.751	1.00150.01
ATOM	1887	CB	LEU	350	23.317	22.709	91.670	1.00150.01
ATOM	1888	CG	LEU	350	22.158	22.234	90.778	1.00150.01
ATOM	1889	CD2	LEU	350	21.987	23.148	89.553	1.00150.01
ATOM	1890	CD1	LEU	350	20.866	22.057	91.587	1.00150.01
ATOM	1891	C	LEU	350	24.986	22.232	93.392	1.00150.01
ATOM	1892	O	LEU	350	24.993	23.291	94.020	1.00150.01
ATOM	1893	N	LYS	351	26.070	21.445	93.267	1.00285.93
ATOM	1894	CA	LYS	351	27.330	21.808	93.827	1.00285.93
ATOM	1895	CB	LYS	351	27.583	21.249	95.236	1.00285.93
ATOM	1896	CG	LYS	351	26.595	21.702	96.300	1.00285.93
ATOM	1897	CD	LYS	351	26.817	21.034	97.659	1.00285.93
ATOM	1898	CE	LYS	351	28.030	21.589	98.414	1.00285.93
ATOM	1899	NZ	LYS	351	28.195	20.882	99.704	1.00285.93
ATOM	1900	C	LYS	351	28.364	21.123	93.007	1.00285.93
ATOM	1901	O	LYS	351	28.060	20.255	92.193	1.00285.93
ATOM	1902	N	LYS	352	29.625	21.540	93.192	1.00262.02
ATOM	1903	CA	LYS	352	30.745	20.865	92.618	1.00262.02
ATOM	1904	CB	LYS	352	31.952	21.787	92.381	1.00262.02
ATOM	1905	CG	LYS	352	31.819	22.672	91.138	1.00262.02
ATOM	1906	CD	LYS	352	30.600	23.594	91.162	1.00262.02
ATOM	1907	CE	LYS	352	29.518	23.209	90.146	1.00262.02
ATOM	1908	NZ	LYS	352	29.188	21.769	90.259	1.00262.02
ATOM	1909	C	LYS	352	31.118	19.856	93.656	1.00262.02

ATOM	1910	O	LYS	352	30.529	19.818	94.732	1.00262.02
ATOM	1911	N	VAL	353	32.064	18.956	93.357	1.00 96.29
ATOM	1912	CA	VAL	353	32.401	18.034	94.396	1.00 96.29
ATOM	1913	CB	VAL	353	33.454	17.048	93.992	1.00 96.29
ATOM	1914	CG1	VAL	353	33.825	16.202	95.221	1.00 96.29
ATOM	1915	CG2	VAL	353	32.929	16.222	92.803	1.00 96.29
ATOM	1916	C	VAL	353	32.962	18.832	95.531	1.00 96.29
ATOM	1917	O	VAL	353	32.568	18.665	96.685	1.00 96.29
ATOM	1918	N	TYR	354	33.900	19.743	95.213	1.00110.82
ATOM	1919	CA	TYR	354	34.573	20.510	96.218	1.00110.82
ATOM	1920	CB	TYR	354	35.752	21.329	95.661	1.00110.82
ATOM	1921	CG	TYR	354	36.565	21.799	96.822	1.00110.82
ATOM	1922	CD1	TYR	354	37.557	20.991	97.328	1.00110.82
ATOM	1923	CD2	TYR	354	36.350	23.026	97.405	1.00110.82
ATOM	1924	CE1	TYR	354	38.322	21.393	98.396	1.00110.82
ATOM	1925	CE2	TYR	354	37.114	23.435	98.475	1.00110.82
ATOM	1926	CZ	TYR	354	38.103	22.620	98.972	1.00110.82
ATOM	1927	OH	TYR	354	38.887	23.040	100.067	1.00110.82
ATOM	1928	C	TYR	354	33.630	21.476	96.875	1.00110.82
ATOM	1929	O	TYR	354	33.613	21.591	98.099	1.00110.82
ATOM	1930	N	THR	355	32.796	22.186	96.086	1.00255.20
ATOM	1931	CA	THR	355	31.997	23.218	96.692	1.00255.20
ATOM	1932	CB	THR	355	32.495	24.598	96.375	1.00255.20
ATOM	1933	OG1	THR	355	32.426	24.834	94.975	1.00255.20
ATOM	1934	CG2	THR	355	33.950	24.725	96.861	1.00255.20
ATOM	1935	C	THR	355	30.593	23.148	96.186	1.00255.20
ATOM	1936	O	THR	355	30.144	22.125	95.686	1.00255.20
ATOM	1937	N	PHE	356	29.847	24.257	96.373	1.00322.17
ATOM	1938	CA	PHE	356	28.493	24.408	95.916	1.00322.17
ATOM	1939	CB	PHE	356	27.639	25.183	96.950	1.00322.17
ATOM	1940	CG	PHE	356	26.183	25.190	96.604	1.00322.17
ATOM	1941	CD1	PHE	356	25.653	26.176	95.805	1.00322.17
ATOM	1942	CD2	PHE	356	25.329	24.227	97.092	1.00322.17
ATOM	1943	CE1	PHE	356	24.315	26.192	95.485	1.00322.17
ATOM	1944	CE2	PHE	356	23.992	24.232	96.779	1.00322.17
ATOM	1945	CZ	PHE	356	23.478	25.217	95.971	1.00322.17
ATOM	1946	C	PHE	356	28.646	25.273	94.705	1.00322.17
ATOM	1947	O	PHE	356	29.539	26.119	94.691	1.00322.17
ATOM	1948	N	PHE	357	27.836	25.084	93.637	1.00120.88
ATOM	1949	CA	PHE	357	28.089	25.979	92.549	1.00120.88
ATOM	1950	CB	PHE	357	27.319	25.680	91.245	1.00120.88
ATOM	1951	CG	PHE	357	25.892	26.079	91.379	1.00120.88
ATOM	1952	CD1	PHE	357	25.525	27.364	91.063	1.00120.88
ATOM	1953	CD2	PHE	357	24.931	25.194	91.801	1.00120.88
ATOM	1954	CE1	PHE	357	24.219	27.770	91.167	1.00120.88
ATOM	1955	CE2	PHE	357	23.623	25.607	91.904	1.00120.88
ATOM	1956	CZ	PHE	357	23.257	26.891	91.590	1.00120.88
ATOM	1957	C	PHE	357	27.698	27.319	93.070	1.00120.88
ATOM	1958	O	PHE	357	26.608	27.501	93.610	1.00120.88
ATOM	1959	N	LYS	358	28.604	28.300	92.942	1.00147.15
ATOM	1960	CA	LYS	358	28.329	29.562	93.552	1.00147.15
ATOM	1961	CB	LYS	358	29.297	29.904	94.692	1.00147.15
ATOM	1962	CG	LYS	358	30.771	29.744	94.321	1.00147.15
ATOM	1963	CD	LYS	358	31.733	30.473	95.261	1.00147.15
ATOM	1964	CE	LYS	358	31.409	30.288	96.743	1.00147.15
ATOM	1965	NZ	LYS	358	30.264	31.151	97.126	1.00147.15
ATOM	1966	C	LYS	358	28.429	30.643	92.538	1.00147.15
ATOM	1967	O	LYS	358	28.609	30.394	91.347	1.00147.15
ATOM	1968	N	PHE	359	28.283	31.889	93.022	1.00116.80
ATOM	1969	CA	PHE	359	28.319	33.059	92.206	1.00116.80
ATOM	1970	CB	PHE	359	27.859	34.340	92.937	1.00116.80
ATOM	1971	CG	PHE	359	28.713	34.619	94.120	1.00116.80
ATOM	1972	CD1	PHE	359	28.456	34.001	95.325	1.00116.80
ATOM	1973	CD2	PHE	359	29.767	35.498	94.036	1.00116.80
ATOM	1974	CE1	PHE	359	29.237	34.255	96.427	1.00116.80
ATOM	1975	CE2	PHE	359	30.549	35.757	95.135	1.00116.80

ATOM	1976	CZ	PHE	359	30.285	35.136	96.333	1.00116.80
ATOM	1977	C	PHE	359	29.687	33.211	91.623	1.00116.80
ATOM	1978	O	PHE	359	29.829	33.701	90.505	1.00116.80
ATOM	1979	N	LEU	360	30.742	32.806	92.360	1.00 80.96
ATOM	1980	CA	LEU	360	32.057	32.919	91.795	1.00 80.96
ATOM	1981	CB	LEU	360	33.203	32.471	92.725	1.00 80.96
ATOM	1982	CG	LEU	360	33.432	33.416	93.923	1.00 80.96
ATOM	1983	CD2	LEU	360	34.798	33.177	94.586	1.00 80.96
ATOM	1984	CD1	LEU	360	32.260	33.365	94.915	1.00 80.96
ATOM	1985	C	LEU	360	32.093	32.064	90.567	1.00 80.96
ATOM	1986	O	LEU	360	32.682	32.447	89.557	1.00 80.96
ATOM	1987	N	ALA	361	31.450	30.882	90.622	1.00 33.90
ATOM	1988	CA	ALA	361	31.404	30.015	89.480	1.00 33.90
ATOM	1989	CB	ALA	361	30.636	28.711	89.746	1.00 33.90
ATOM	1990	C	ALA	361	30.683	30.761	88.399	1.00 33.90
ATOM	1991	O	ALA	361	31.024	30.680	87.220	1.00 33.90
ATOM	1992	N	ASP	362	29.652	31.531	88.776	1.00 92.51
ATOM	1993	CA	ASP	362	28.901	32.266	87.801	1.00 92.51
ATOM	1994	CB	ASP	362	27.776	33.095	88.461	1.00 92.51
ATOM	1995	CG	ASP	362	26.929	33.822	87.417	1.00 92.51
ATOM	1996	OD1	ASP	362	27.501	34.539	86.554	1.00 92.51
ATOM	1997	OD2	ASP	362	25.681	33.659	87.473	1.00 92.51
ATOM	1998	C	ASP	362	29.829	33.214	87.101	1.00 92.51
ATOM	1999	O	ASP	362	29.778	33.357	85.880	1.00 92.51
ATOM	2000	N	LYS	363	30.713	33.889	87.858	1.00102.78
ATOM	2001	CA	LYS	363	31.580	34.866	87.261	1.00102.78
ATOM	2002	CB	LYS	363	32.441	35.585	88.315	1.00102.78
ATOM	2003	CG	LYS	363	33.389	36.645	87.750	1.00102.78
ATOM	2004	CD	LYS	363	33.968	37.566	88.828	1.00102.78
ATOM	2005	CE	LYS	363	35.188	38.365	88.370	1.00102.78
ATOM	2006	NZ	LYS	363	36.386	37.488	88.348	1.00102.78
ATOM	2007	C	LYS	363	32.496	34.220	86.264	1.00102.78
ATOM	2008	O	LYS	363	32.609	34.680	85.129	1.00102.78
ATOM	2009	N	LYS	364	33.170	33.120	86.648	1.00 86.80
ATOM	2010	CA	LYS	364	34.086	32.497	85.736	1.00 86.80
ATOM	2011	CB	LYS	364	35.057	31.490	86.379	1.00 86.80
ATOM	2012	CG	LYS	364	36.209	32.158	87.136	1.00 86.80
ATOM	2013	CD	LYS	364	37.021	31.212	88.023	1.00 86.80
ATOM	2014	CE	LYS	364	36.440	31.043	89.428	1.00 86.80
ATOM	2015	NZ	LYS	364	37.385	30.291	90.284	1.00 86.80
ATOM	2016	C	LYS	364	33.344	31.863	84.602	1.00 86.80
ATOM	2017	O	LYS	364	33.873	31.749	83.498	1.00 86.80
ATOM	2018	N	MET	365	32.092	31.429	84.831	1.00 53.49
ATOM	2019	CA	MET	365	31.359	30.755	83.796	1.00 53.49
ATOM	2020	CB	MET	365	29.982	30.264	84.255	1.00 53.49
ATOM	2021	CG	MET	365	29.226	29.461	83.196	1.00 53.49
ATOM	2022	SD	MET	365	29.905	27.805	82.885	1.00 53.49
ATOM	2023	CE	MET	365	28.617	27.319	81.701	1.00 53.49
ATOM	2024	C	MET	365	31.170	31.664	82.625	1.00 53.49
ATOM	2025	O	MET	365	31.208	31.220	81.478	1.00 53.49
ATOM	2026	N	THR	366	30.951	32.966	82.866	1.00 70.35
ATOM	2027	CA	THR	366	30.705	33.792	81.730	1.00 70.35
ATOM	2028	CB	THR	366	30.255	35.162	82.075	1.00 70.35
ATOM	2029	OG1	THR	366	29.230	35.112	83.058	1.00 70.35
ATOM	2030	CG2	THR	366	29.616	35.667	80.778	1.00 70.35
ATOM	2031	C	THR	366	31.948	33.865	80.887	1.00 70.35
ATOM	2032	O	THR	366	31.868	33.895	79.660	1.00 70.35
ATOM	2033	N	LEU	367	33.136	33.919	81.526	1.00 81.70
ATOM	2034	CA	LEU	367	34.382	33.971	80.809	1.00 81.70
ATOM	2035	CB	LEU	367	35.609	34.150	81.721	1.00 81.70
ATOM	2036	CG	LEU	367	35.688	35.525	82.413	1.00 81.70
ATOM	2037	CD2	LEU	367	37.070	35.740	83.050	1.00 81.70
ATOM	2038	CD1	LEU	367	34.531	35.733	83.400	1.00 81.70
ATOM	2039	C	LEU	367	34.564	32.683	80.071	1.00 81.70
ATOM	2040	O	LEU	367	35.063	32.663	78.947	1.00 81.70
ATOM	2041	N	PHE	368	34.163	31.566	80.708	1.00 59.75

ATOM	2042	CA	PHE	368	34.302	30.249	80.153	1.00 59.75
ATOM	2043	CB	PHE	368	33.778	29.185	81.136	1.00 59.75
ATOM	2044	CG	PHE	368	33.868	27.826	80.529	1.00 59.75
ATOM	2045	CD1	PHE	368	35.075	27.174	80.426	1.00 59.75
ATOM	2046	CD2	PHE	368	32.731	27.191	80.091	1.00 59.75
ATOM	2047	CE1	PHE	368	35.143	25.915	79.873	1.00 59.75
ATOM	2048	CE2	PHE	368	32.792	25.932	79.538	1.00 59.75
ATOM	2049	CZ	PHE	368	34.003	25.293	79.427	1.00 59.75
ATOM	2050	C	PHE	368	33.512	30.169	78.886	1.00 59.75
ATOM	2051	O	PHE	368	34.011	29.728	77.853	1.00 59.75
ATOM	2052	N	LYS	369	32.250	30.623	78.918	1.00110.95
ATOM	2053	CA	LYS	369	31.446	30.530	77.736	1.00110.95
ATOM	2054	CB	LYS	369	30.015	31.029	77.952	1.00110.95
ATOM	2055	CG	LYS	369	29.190	30.880	76.683	1.00110.95
ATOM	2056	CD	LYS	369	27.688	30.943	76.907	1.00110.95
ATOM	2057	CE	LYS	369	26.937	30.514	75.656	1.00110.95
ATOM	2058	NZ	LYS	369	27.482	29.223	75.183	1.00110.95
ATOM	2059	C	LYS	369	32.063	31.367	76.659	1.00110.95
ATOM	2060	O	LYS	369	32.098	30.975	75.494	1.00110.95
ATOM	2061	N	SER	370	32.579	32.549	77.028	1.00 75.96
ATOM	2062	CA	SER	370	33.162	33.448	76.078	1.00 75.96
ATOM	2063	CB	SER	370	33.710	34.714	76.757	1.00 75.96
ATOM	2064	OG	SER	370	34.387	35.523	75.810	1.00 75.96
ATOM	2065	C	SER	370	34.315	32.775	75.399	1.00 75.96
ATOM	2066	O	SER	370	34.474	32.884	74.184	1.00 75.96
ATOM	2067	N	ILE	371	35.154	32.052	76.163	1.00124.77
ATOM	2068	CA	ILE	371	36.307	31.439	75.569	1.00124.77
ATOM	2069	CB	ILE	371	37.271	30.824	76.546	1.00124.77
ATOM	2070	CG2	ILE	371	36.641	29.548	77.119	1.00124.77
ATOM	2071	CG1	ILE	371	38.620	30.560	75.853	1.00124.77
ATOM	2072	CD1	ILE	371	39.348	31.834	75.428	1.00124.77
ATOM	2073	C	ILE	371	35.882	30.387	74.597	1.00124.77
ATOM	2074	O	ILE	371	36.477	30.250	73.530	1.00124.77
ATOM	2075	N	LEU	372	34.838	29.605	74.927	1.00105.73
ATOM	2076	CA	LEU	372	34.451	28.565	74.019	1.00105.73
ATOM	2077	CB	LEU	372	33.292	27.682	74.510	1.00105.73
ATOM	2078	CG	LEU	372	33.737	26.614	75.522	1.00105.73
ATOM	2079	CD2	LEU	372	32.585	25.650	75.845	1.00105.73
ATOM	2080	CD1	LEU	372	34.372	27.235	76.772	1.00105.73
ATOM	2081	C	LEU	372	34.060	29.165	72.714	1.00105.73
ATOM	2082	O	LEU	372	34.364	28.606	71.662	1.00105.73
ATOM	2083	N	PHE	373	33.365	30.314	72.732	1.00 64.70
ATOM	2084	CA	PHE	373	32.945	30.855	71.478	1.00 64.70
ATOM	2085	CB	PHE	373	31.996	32.050	71.593	1.00 64.70
ATOM	2086	CG	PHE	373	31.471	32.113	70.211	1.00 64.70
ATOM	2087	CD1	PHE	373	30.661	31.089	69.784	1.00 64.70
ATOM	2088	CD2	PHE	373	31.779	33.147	69.361	1.00 64.70
ATOM	2089	CE1	PHE	373	30.154	31.086	68.513	1.00 64.70
ATOM	2090	CE2	PHE	373	31.269	33.146	68.086	1.00 64.70
ATOM	2091	CZ	PHE	373	30.458	32.118	67.664	1.00 64.70
ATOM	2092	C	PHE	373	34.131	31.280	70.664	1.00 64.70
ATOM	2093	O	PHE	373	34.206	30.989	69.472	1.00 64.70
ATOM	2094	N	ASN	374	35.105	31.971	71.286	1.00 35.72
ATOM	2095	CA	ASN	374	36.247	32.451	70.559	1.00 35.72
ATOM	2096	CB	ASN	374	37.207	33.269	71.437	1.00 35.72
ATOM	2097	CG	ASN	374	36.483	34.537	71.865	1.00 35.72
ATOM	2098	OD1	ASN	374	35.692	35.105	71.114	1.00 35.72
ATOM	2099	ND2	ASN	374	36.758	34.995	73.115	1.00 35.72
ATOM	2100	C	ASN	374	37.011	31.277	70.026	1.00 35.72
ATOM	2101	O	ASN	374	37.540	31.315	68.917	1.00 35.72
ATOM	2102	N	LEU	375	37.099	30.205	70.833	1.00138.95
ATOM	2103	CA	LEU	375	37.815	29.003	70.512	1.00138.95
ATOM	2104	CB	LEU	375	37.964	28.066	71.731	1.00138.95
ATOM	2105	CG	LEU	375	38.995	26.926	71.570	1.00138.95
ATOM	2106	CD2	LEU	375	40.379	27.498	71.223	1.00138.95
ATOM	2107	CD1	LEU	375	38.548	25.833	70.589	1.00138.95

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ATOM   2108  C   LEU   375      37.093  28.291  69.406  1.00138.95
ATOM   2109  O   LEU   375      37.711  27.552  68.641  1.00138.95
ATOM   2110  N   HIS   376      35.766  28.517  69.292  1.00123.01
ATOM   2111  CA  HIS   376      34.901  27.828  68.370  1.00123.01
ATOM   2112  ND1 HIS   376      36.992  27.064  65.722  1.00123.01
ATOM   2113  CG  HIS   376      36.407  28.177  66.282  1.00123.01
ATOM   2114  CB  HIS   376      35.031  28.206  66.871  1.00123.01
ATOM   2115  NE2 HIS   376      38.477  28.713  65.561  1.00123.01
ATOM   2116  CD2 HIS   376      37.327  29.175  66.176  1.00123.01
ATOM   2117  CE1 HIS   376      38.228  27.440  65.307  1.00123.01
ATOM   2118  C   HIS   376      35.014  26.360  68.605  1.00123.01
ATOM   2119  O   HIS   376      35.402  25.581  67.735  1.00123.01
ATOM   2120  N   ASP   377      34.645  25.976  69.845  1.00 65.93
ATOM   2121  CA  ASP   377      34.668  24.635  70.353  1.00 65.93
ATOM   2122  CB  ASP   377      34.286  24.519  71.842  1.00 65.93
ATOM   2123  CG  ASP   377      35.531  24.786  72.676  1.00 65.93
ATOM   2124  OD1 ASP   377      36.651  24.598  72.132  1.00 65.93
ATOM   2125  OD2 ASP   377      35.380  25.159  73.869  1.00 65.93
ATOM   2126  C   ASP   377      33.737  23.760  69.578  1.00 65.93
ATOM   2127  O   ASP   377      33.945  22.551  69.506  1.00 65.93
ATOM   2128  N   LEU   378      32.671  24.325  68.988  1.00 87.86
ATOM   2129  CA  LEU   378      31.748  23.489  68.277  1.00 87.86
ATOM   2130  CB  LEU   378      30.589  24.271  67.642  1.00 87.86
ATOM   2131  CG  LEU   378      29.593  24.813  68.680  1.00 87.86
ATOM   2132  CD2 LEU   378      30.294  25.697  69.726  1.00 87.86
ATOM   2133  CD1 LEU   378      28.792  23.673  69.319  1.00 87.86
ATOM   2134  C   LEU   378      32.477  22.779  67.182  1.00 87.86
ATOM   2135  O   LEU   378      32.211  21.606  66.929  1.00 87.86
ATOM   2136  N   SER   379      33.403  23.460  66.483  1.00 17.91
ATOM   2137  CA  SER   379      34.122  22.754  65.465  1.00 17.91
ATOM   2138  CB  SER   379      34.647  23.656  64.331  1.00 17.91
ATOM   2139  OG  SER   379      35.608  24.576  64.827  1.00 17.91
ATOM   2140  C   SER   379      35.317  22.106  66.145  1.00 17.91
ATOM   2141  O   SER   379      36.181  22.858  66.669  1.00 17.91
ATOM   2142  OXT SER   379      35.380  20.848  66.153  1.00 17.91
END
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TABLE-3

REMARK 4
REMARK TTP-A Computed low-energy docking mode-1
REMARK Free Energy of Binding = -11.24 kcal/mol

ATOM	1	C9	MOL	1	14.331	35.024	76.250	-0.49
ATOM	2	C4	MOL	1	15.175	35.446	77.272	-0.50
ATOM	3	C12	MOL	1	14.648	35.356	74.948	-0.41
ATOM	4	C1	MOL	1	16.340	36.195	77.047	-0.52
ATOM	5	C3	MOL	1	16.661	36.522	75.696	-0.49
ATOM	6	C7	MOL	1	15.793	36.088	74.698	-0.42
ATOM	7	C14	MOL	1	13.069	34.215	76.522	-0.35
ATOM	8	C16	MOL	1	12.147	35.063	77.449	-0.61
ATOM	9	N17	MOL	1	10.746	34.939	77.134	-0.19
ATOM	10	H17	MOL	1	10.090	34.523	77.810	-0.19
ATOM	11	C18	MOL	1	10.294	35.400	75.880	-0.47
ATOM	12	O20	MOL	1	11.112	35.909	75.103	+0.04
ATOM	13	C19	MOL	1	8.875	35.299	75.453	-0.39
ATOM	14	C22	MOL	1	8.475	34.568	74.332	-0.31
ATOM	15	O25	MOL	1	9.402	33.882	73.533	-0.10
ATOM	16	H25	MOL	1	9.655	33.026	73.978	-0.14
ATOM	17	C24	MOL	1	7.129	34.514	73.990	-0.26
ATOM	18	C30	MOL	1	3.884	35.791	75.169	-0.09
ATOM	19	C28	MOL	1	4.833	35.121	74.403	-0.13
ATOM	20	C27	MOL	1	5.623	36.575	76.636	-0.25
ATOM	21	C29	MOL	1	4.281	36.517	76.287	-0.15
ATOM	22	C26	MOL	1	6.177	35.180	74.753	-0.18
ATOM	23	C23	MOL	1	6.572	35.908	75.868	-0.27
ATOM	24	C21	MOL	1	7.916	35.963	76.214	-0.39
ATOM	25	C2	MOL	1	17.063	36.529	78.390	-0.54
ATOM	26	C6	MOL	1	17.552	35.601	79.301	-0.75
ATOM	27	C11	MOL	1	18.194	35.978	80.472	-0.84
ATOM	28	C15	MOL	1	18.364	37.322	80.761	-0.83
ATOM	29	N1	MOL	1	19.005	37.698	81.944	-0.59
ATOM	30	O2	MOL	1	18.437	38.366	82.727	-0.29
ATOM	31	O3	MOL	1	20.246	37.308	82.183	-0.77
ATOM	32	C10	MOL	1	17.889	38.277	79.867	-0.73
ATOM	33	C5	MOL	1	17.251	37.877	78.694	-0.60
ATOM	34	O8	MOL	1	17.778	37.255	75.046	+0.02
ATOM	35	C13	MOL	1	17.743	38.555	74.504	-0.36

END
REMARK TTP-A Computed low-energy docking mode-2
REMARK Free Energy of Binding = -11.24 kcal/mol

ATOM	1	C9	MOL	2	14.546	35.957	75.646	-0.41
ATOM	2	C4	MOL	2	15.319	36.210	76.776	-0.43
ATOM	3	C12	MOL	2	14.848	36.618	74.473	-0.33
ATOM	4	C1	MOL	2	16.397	37.106	76.783	-0.49
ATOM	5	C3	MOL	2	16.705	37.776	75.560	-0.43
ATOM	6	C7	MOL	2	15.909	37.503	74.451	-0.35
ATOM	7	C14	MOL	2	13.377	34.979	75.667	-0.40
ATOM	8	C16	MOL	2	12.063	35.802	75.507	-0.40
ATOM	9	N17	MOL	2	10.877	34.985	75.452	-0.12
ATOM	10	H17	MOL	2	10.840	34.151	74.849	+0.28
ATOM	11	C18	MOL	2	9.769	35.352	76.244	-0.52
ATOM	12	O20	MOL	2	9.861	36.351	76.969	-0.12
ATOM	13	C19	MOL	2	8.495	34.588	76.243	-0.49
ATOM	14	C22	MOL	2	7.581	34.648	75.187	-0.31
ATOM	15	O25	MOL	2	7.816	35.443	74.057	+0.13
ATOM	16	H25	MOL	2	8.798	35.512	73.896	+0.11
ATOM	17	C24	MOL	2	6.408	33.905	75.251	-0.29
ATOM	18	C30	MOL	2	4.690	31.567	77.516	-0.33
ATOM	19	C28	MOL	2	4.959	32.366	76.409	-0.31
ATOM	20	C27	MOL	2	6.774	32.243	78.510	-0.59
ATOM	21	C29	MOL	2	5.599	31.506	78.566	-0.47
ATOM	22	C26	MOL	2	6.135	33.104	76.354	-0.36
ATOM	23	C23	MOL	2	7.042	33.044	77.405	-0.54
ATOM	24	C21	MOL	2	8.216	33.783	77.344	-0.53

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ATOM     25  C2  MOL     2      17.054  37.186  78.197    -0.46
ATOM     26  C6  MOL     2      17.338  36.106  79.022    -0.65
ATOM     27  C11 MOL     2      17.934  36.258  80.266    -0.82
ATOM     28  C15 MOL     2      18.266  37.524  80.719    -0.82
ATOM     29  N1  MOL     2      18.860  37.674  81.974    -0.55
ATOM     30  O2  MOL     2      18.306  38.286  82.812    -0.23
ATOM     31  O3  MOL     2      20.042  37.134  82.222    -0.76
ATOM     32  C10 MOL     2      17.999  38.628  79.915    -0.61
ATOM     33  C5  MOL     2      17.404  38.452  78.666    -0.61
ATOM     34  O8  MOL     2      17.746  38.753  75.149    +0.00
ATOM     35  C13 MOL     2      17.705  40.154  75.297    -0.29
END
REMARK   TTP-A Computed low-energy docking mode-3
REMARK   Free Energy of Binding    =  -11.24 kcal/mol
ATOM      1  C9  MOL     3      17.997  38.677  73.823    -0.35
ATOM      2  C4  MOL     3      17.513  37.647  74.624    -0.35
ATOM      3  C12 MOL     3      18.452  39.831  74.429    -0.29
ATOM      4  C1  MOL     3      17.465  37.720  76.024    -0.42
ATOM      5  C3  MOL     3      17.948  38.915  76.638    -0.44
ATOM      6  C7  MOL     3      18.421  39.927  75.807    -0.39
ATOM      7  C14 MOL     3      18.036  38.573  72.304    -0.34
ATOM      8  C16 MOL     3      16.629  38.966  71.761    -0.19
ATOM      9  N17 MOL     3      15.601  38.008  72.082    -0.28
ATOM     10  H17 MOL     3      15.740  37.005  71.896    -0.22
ATOM     11  C18 MOL     3      14.401  38.475  72.657    -0.15
ATOM     12  O20 MOL     3      14.280  39.687  72.881    +0.17
ATOM     13  C19 MOL     3      13.274  37.571  73.004    -0.17
ATOM     14  C22 MOL     3      12.524  36.896  72.038    -0.16
ATOM     15  O25 MOL     3      12.793  37.037  70.669    +0.18
ATOM     16  H25 MOL     3      13.755  36.838  70.497    +0.10
ATOM     17  C24 MOL     3      11.483  36.064  72.434    -0.22
ATOM     18  C30 MOL     3       9.839  34.901  75.515    -0.38
ATOM     19  C28 MOL     3      10.138  35.063  74.166    -0.24
ATOM     20  C27 MOL     3      11.629  36.404  76.092    -0.38
ATOM     21  C29 MOL     3      10.587  35.572  76.478    -0.54
ATOM     22  C26 MOL     3      11.181  35.897  73.780    -0.26
ATOM     23  C23 MOL     3      11.925  36.568  74.743    -0.30
ATOM     24  C21 MOL     3      12.967  37.399  74.351    -0.25
ATOM     25  C2  MOL     3      16.858  36.418  76.636    -0.54
ATOM     26  C6  MOL     3      17.578  35.307  77.056    -0.61
ATOM     27  C11 MOL     3      16.964  34.188  77.600    -0.64
ATOM     28  C15 MOL     3      15.586  34.159  77.739    -0.69
ATOM     29  N1  MOL     3      14.972  33.028  78.281    -0.52
ATOM     30  O2  MOL     3      14.651  33.025  79.413    -0.21
ATOM     31  O3  MOL     3      14.752  31.962  77.529    -0.27
ATOM     32  C10 MOL     3      14.836  35.257  77.331    -0.54
ATOM     33  C5  MOL     3      15.473  36.374  76.791    -0.43
ATOM     34  O8  MOL     3      18.089  39.372  78.044    -0.15
ATOM     35  C13 MOL     3      17.310  38.979  79.150    -0.69
END
REMARK   TTP-A Computed low-energy docking mode-4
REMARK   Free Energy of Binding    =  -11.24 kcal/mol
ATOM      1  C9  MOL     4      10.690  36.976  72.708    -0.14
ATOM      2  C4  MOL     4       9.929  36.252  73.621    -0.21
ATOM      3  C12 MOL     4      10.923  38.314  72.951    -0.11
ATOM      4  C1  MOL     4       9.385  36.815  74.784    -0.25
ATOM      5  C3  MOL     4       9.642  38.198  75.029    -0.27
ATOM      6  C7  MOL     4      10.402  38.893  74.093    -0.18
ATOM      7  C14 MOL     4      11.267  36.340  71.449    -0.17
ATOM      8  C16 MOL     4      12.241  35.206  71.890    -0.28
ATOM      9  N17 MOL     4      12.937  35.491  73.119    -0.17
ATOM     10  H17 MOL     4      12.485  36.039  73.864    +0.10
ATOM     11  C18 MOL     4      14.251  35.003  73.278    -0.27
ATOM     12  O20 MOL     4      14.751  34.334  72.365    -0.29
ATOM     13  C19 MOL     4      15.059  35.261  74.498    -0.42
ATOM     14  C22 MOL     4      16.165  36.114  74.503    -0.41
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ATOM     15  O25 MOL     4      16.584  36.781  73.342   -0.21
ATOM     16  H25 MOL     4      15.824  36.835  72.698   -0.17
ATOM     17  C24 MOL     4      16.876  36.310  75.681   -0.50
ATOM     18  C30 MOL     4      16.832  35.223  79.197   -0.76
ATOM     19  C28 MOL     4      17.215  35.870  78.027   -0.58
ATOM     20  C27 MOL     4      15.013  34.174  78.022   -0.74
ATOM     21  C29 MOL     4      15.729  34.375  79.194   -0.69
ATOM     22  C26 MOL     4      16.497  35.667  76.854   -0.55
ATOM     23  C23 MOL     4      15.397  34.818  76.851   -0.55
ATOM     24  C21 MOL     4      14.683  34.621  75.676   -0.45
ATOM     25  C2  MOL     4       8.571  35.757  75.595   -0.37
ATOM     26  C6  MOL     4       7.192  35.599  75.566   -0.28
ATOM     27  C11 MOL     4       6.540  34.626  76.311   -0.35
ATOM     28  C15 MOL     4       7.275  33.771  77.117   -0.52
ATOM     29  N1  MOL     4       6.615  32.797  77.870   -0.34
ATOM     30  O2  MOL     4       6.313  33.026  78.983   -0.12
ATOM     31  O3  MOL     4       6.333  31.619  77.337   -0.05
ATOM     32  C10 MOL     4       8.659  33.901  77.165   -0.44
ATOM     33  C5  MOL     4       9.294  34.882  76.405   -0.52
ATOM     34  O8  MOL     4       9.280  39.141  76.118   -0.03
ATOM     35  C13 MOL     4       8.017  39.717  76.363   -0.25
END
REMARK   TTP-A Computed low-energy docking mode-5
REMARK   Free Energy of Binding     =  -11.24 kcal/mol
ATOM      1  C9  MOL     5      13.105  36.487  73.198   -0.23
ATOM      2  C4  MOL     5      11.920  36.000  72.657   -0.23
ATOM      3  C12 MOL     5      13.046  37.547  74.081   -0.23
ATOM      4  C1  MOL     5      10.659  36.532  72.965   -0.18
ATOM      5  C3  MOL     5      10.612  37.621  73.887   -0.18
ATOM      6  C7  MOL     5      11.817  38.087  74.405   -0.18
ATOM      7  C14 MOL     5      14.463  35.893  72.844   -0.13
ATOM      8  C16 MOL     5      14.872  34.918  73.989   -0.37
ATOM      9  N17 MOL     5      15.745  35.515  74.967   -0.28
ATOM     10  H17 MOL     5      16.727  35.724  74.738   -0.00
ATOM     11  C18 MOL     5      15.225  35.808  76.245   -0.45
ATOM     12  O20 MOL     5      14.035  35.558  76.475   -0.04
ATOM     13  C19 MOL     5      16.049  36.404  77.329   -0.46
ATOM     14  C22 MOL     5      16.163  37.784  77.517   -0.33
ATOM     15  O25 MOL     5      15.500  38.696  76.683   -0.02
ATOM     16  H25 MOL     5      14.531  38.465  76.641   +0.09
ATOM     17  C24 MOL     5      16.951  38.273  78.552   -0.62
ATOM     18  C30 MOL     5      19.086  37.030  81.280   -0.78
ATOM     19  C28 MOL     5      18.412  37.904  80.433   -0.77
ATOM     20  C27 MOL     5      18.187  35.158  80.063   -0.78
ATOM     21  C29 MOL     5      18.972  35.656  81.094   -0.67
ATOM     22  C26 MOL     5      17.626  37.405  79.401   -0.59
ATOM     23  C23 MOL     5      17.515  36.032  79.216   -0.67
ATOM     24  C21 MOL     5      16.727  35.539  78.184   -0.65
ATOM     25  C2  MOL     5       9.528  35.786  72.190   -0.19
ATOM     26  C6  MOL     5       9.139  36.037  70.880   -0.13
ATOM     27  C11 MOL     5       8.127  35.322  70.256   -0.06
ATOM     28  C15 MOL     5       7.470  34.317  70.946   -0.22
ATOM     29  N1  MOL     5       6.448  33.603  70.316   -0.41
ATOM     30  O2  MOL     5       5.410  34.120  70.120   +0.13
ATOM     31  O3  MOL     5       6.642  32.348  69.943   -0.23
ATOM     32  C10 MOL     5       7.838  34.037  72.258   -0.34
ATOM     33  C5  MOL     5       8.860  34.764  72.865   -0.31
ATOM     34  O8  MOL     5       9.514  38.430  74.478   +0.14
ATOM     35  C13 MOL     5       8.926  38.269  75.749   -0.34
END
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Table-4

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REMARK    4
REMARK Computed Free energy of binding = -10.68kcal/mol
REMARK TTP-B Computed low-energy docking mode-1
ATOM      1  C1  TTB     1      16.460  36.607  76.845 -0.00  0.51
ATOM      2  C3  TTB     1      15.068  36.607  76.816 -0.00  0.27
ATOM      3  C4  TTB     1      17.148  35.418  77.039 -0.00  0.61
ATOM      4  C7  TTB     1      14.360  35.417  76.974 -0.00  0.51
ATOM      5  C8  TTB     1      16.447  34.230  77.202 -0.00  0.66
ATOM      6  C12 TTB     1      15.058  34.223  77.169 -0.00  0.63
ATOM      7  C2  TTB     1      17.213  37.852  76.663 -0.00  0.48
ATOM      8  C5  TTB     1      17.535  38.651  77.755 -0.00  0.51
ATOM      9  C9  TTB     1      18.241  39.834  77.565 -0.00  0.51
ATOM     10  C13 TTB     1      18.621  40.220  76.284 -0.00  0.44
ATOM     11  C   TTB     1      19.378  41.498  76.076 -0.00  0.34
ATOM     12  F2  TTB     1      19.510  42.182  77.268 -0.00  0.28
ATOM     13  F3  TTB     1      20.635  41.175  75.610 -0.00  0.35
ATOM     14  F4  TTB     1      18.761  42.258  75.105 -0.00  0.12
ATOM     15  C10 TTB     1      18.301  39.422  75.193 -0.00  0.36
ATOM     16  C6  TTB     1      17.596  38.240  75.383 -0.00  0.40
ATOM     17  C11 TTB     1      12.874  35.461  76.923 -0.00  0.57
ATOM     18  O15 TTB     1      12.223  34.713  77.662 -0.00  0.12
ATOM     19  N14 TTB     1      12.209  36.345  76.056 -0.00  0.26
ATOM     20  C17 TTB     1      10.796  36.441  76.065 -0.00  0.46
ATOM     21  C18 TTB     1      10.270  35.386  75.053 -0.00  0.34
ATOM     22  C20 TTB     1       9.070  34.590  75.558 -0.00  0.42
ATOM     23  C23 TTB     1       7.858  34.704  74.888 -0.00  0.30
ATOM     24  C26 TTB     1       6.751  33.978  75.314 -0.00  0.29
ATOM     25  C28 TTB     1       6.852  33.133  76.413 -0.00  0.37
ATOM     26  C29 TTB     1       5.684  32.375  76.857 -0.00  0.37
ATOM     27  C30 TTB     1       4.745  32.975  77.688 -0.00  0.28
ATOM     28  C32 TTB     1       3.634  32.260  78.113 -0.00  0.21
ATOM     29  C34 TTB     1       3.460  30.940  77.709 -0.00  0.27
ATOM     30  F36 TTB     1       2.387  30.249  78.123 -0.00  0.18
ATOM     31  C33 TTB     1       4.397  30.339  76.879 -0.00  0.43
ATOM     32  C31 TTB     1       5.510  31.056  76.451 -0.00  0.47
ATOM     33  C27 TTB     1       8.062  33.011  77.085 -0.00  0.43
ATOM     34  C24 TTB     1       9.168  33.737  76.656 -0.00  0.47
ATOM     35  C19 TTB     1      10.463  37.836  75.633 -0.00  0.21
ATOM     36  O22 TTB     1      11.083  38.357  74.697  0.00  0.09
ATOM     37  O21 TTB     1       9.471  38.542  76.299 -0.00  0.06
ATOM     38  C25 TTB     1       9.019  39.626  75.493 -0.00  0.28
ATOM     39  O16 TTB     1      14.394  33.003  77.335 -0.00  0.15
ATOM     40  H14 TTB     1      12.755  36.931  75.407  0.00  0.09
ATOM     41  H16 TTB     1      14.333  32.541  76.458  0.00  0.03
END
REMARK    4
REMARK TTP-B Computed low-energy docking mode-2
REMARK Computed Free energy of binding = -9.51kcal/mol
ATOM      1  C1  TTB     2      11.151  36.020  75.575 -0.00  0.41
ATOM      2  C3  TTB     2      10.922  35.738  74.231 -0.00  0.28
ATOM      3  C4  TTB     2      10.133  36.554  76.352 -0.00  0.50
ATOM      4  C7  TTB     2       9.674  35.983  73.662 -0.00  0.22
ATOM      5  C8  TTB     2       8.888  36.804  75.789 -0.00  0.37
ATOM      6  C12 TTB     2       8.654  36.520  74.449 -0.00  0.20
ATOM      7  C2  TTB     2      12.456  35.751  76.186 -0.00  0.49
ATOM      8  C5  TTB     2      12.595  34.762  77.154 -0.00  0.54
ATOM      9  C9  TTB     2      13.838  34.526  77.732 -0.00  0.65
ATOM     10  C13 TTB     2      14.940  35.280  77.344 -0.00  0.53
ATOM     11  C   TTB     2      16.280  35.031  77.970 -0.00  0.65
ATOM     12  F2  TTB     2      17.004  36.205  78.046 -0.00  0.44
ATOM     13  F3  TTB     2      16.070  34.559  79.248 -0.00  0.54
ATOM     14  F4  TTB     2      16.951  34.050  77.273 -0.00  0.52
ATOM     15  C10 TTB     2      14.803  36.268  76.377 -0.00  0.42
ATOM     16  C6  TTB     2      13.562  36.503  75.799 -0.00  0.37
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ATOM     17  C11 TTB     2       9.471  35.654  72.225 -0.00  0.20
ATOM     18  O15 TTB     2       9.001  34.550  71.921 -0.00  0.23
ATOM     19  N14 TTB     2       9.794  36.582  71.220 -0.00  0.12
ATOM     20  C17 TTB     2       9.527  36.296  69.859 -0.00  0.12
ATOM     21  C18 TTB     2      10.801  36.688  69.061 -0.00  0.11
ATOM     22  C20 TTB     2      11.963  35.716  69.239 -0.00  0.17
ATOM     23  C23 TTB     2      12.818  35.881  70.323 -0.00  0.22
ATOM     24  C26 TTB     2      13.876  35.001  70.522 -0.00  0.30
ATOM     25  C28 TTB     2      14.084  33.950  69.636 -0.00  0.31
ATOM     26  C29 TTB     2      15.200  33.030  69.849 -0.00  0.40
ATOM     27  C30 TTB     2      16.254  32.999  68.944 -0.00  0.39
ATOM     28  C32 TTB     2      17.316  32.127  69.141 -0.00  0.48
ATOM     29  C34 TTB     2      17.326  31.282  70.245 -0.00  0.62
ATOM     30  F36 TTB     2      18.351  30.438  70.433 -0.00  0.52
ATOM     31  C33 TTB     2      16.273  31.311  71.152 -0.00  0.62
ATOM     32  C31 TTB     2      15.209  32.185  70.955 -0.00  0.51
ATOM     33  C27 TTB     2      13.232  33.776  68.553 -0.00  0.06
ATOM     34  C24 TTB     2      12.173  34.657  68.357 -0.00  0.15
ATOM     35  C19 TTB     2       8.350  37.140  69.473 -0.00  0.07
ATOM     36  O22 TTB     2       8.431  38.373  69.525  0.00  0.23
ATOM     37  O21 TTB     2       7.170  36.528  69.074  0.00  0.20
ATOM     38  C25 TTB     2       6.157  36.738  70.054 -0.00  0.04
ATOM     39  O16 TTB     2       7.384  36.786  73.924  0.00  0.19
ATOM     40  H14 TTB     2      10.230  37.479  71.476  0.00  0.12
ATOM     41  H16 TTB     2       6.855  35.946  73.905  0.00  0.11
END
REMARK   4
REMARK TTP-B Computed low-energy docking mode-3
REMARK Computed Free energy of binding = -9.72kcal/mol
ATOM      1  C1  TTB     3      16.497  36.818  77.723 -0.00  0.50
ATOM      2  C3  TTB     3      15.398  36.382  76.989 -0.00  0.37
ATOM      3  C4  TTB     3      16.865  36.149  78.882 -0.00  0.68
ATOM      4  C7  TTB     3      14.666  35.272  77.408 -0.00  0.52
ATOM      5  C8  TTB     3      16.137  35.044  79.305 -0.00  0.74
ATOM      6  C12 TTB     3      15.041  34.602  78.574 -0.00  0.72
ATOM      7  C2  TTB     3      17.281  37.975  77.281 -0.00  0.43
ATOM      8  C5  TTB     3      17.913  37.972  76.042 -0.00  0.20
ATOM      9  C9  TTB     3      18.662  39.074  75.642 -0.00  0.26
ATOM     10  C13 TTB     3      18.782  40.175  76.482 -0.00  0.47
ATOM     11  C   TTB     3      19.594  41.362  76.055 -0.00  0.37
ATOM     12  F2  TTB     3      19.158  42.503  76.698 -0.00  0.23
ATOM     13  F3  TTB     3      20.905  41.128  76.411 -0.00  0.39
ATOM     14  F4  TTB     3      19.556  41.491  74.683 -0.00  0.18
ATOM     15  C10 TTB     3      18.150  40.181  77.719 -0.00  0.43
ATOM     16  C6  TTB     3      17.402  39.081  78.118 -0.00  0.61
ATOM     17  C11 TTB     3      13.506  34.832  76.586 -0.00  0.54
ATOM     18  O15 TTB     3      13.425  33.646  76.245  0.00  0.14
ATOM     19  N14 TTB     3      12.506  35.744  76.206 -0.00  0.31
ATOM     20  C17 TTB     3      11.364  35.307  75.490 -0.00  0.35
ATOM     21  C18 TTB     3      11.085  36.377  74.398 -0.00  0.27
ATOM     22  C20 TTB     3      12.345  36.921  73.732 -0.00  0.22
ATOM     23  C23 TTB     3      13.086  36.082  72.908 -0.00  0.25
ATOM     24  C26 TTB     3      14.229  36.554  72.273 -0.00  0.15
ATOM     25  C28 TTB     3      14.638  37.870  72.458 -0.00  0.18
ATOM     26  C29 TTB     3      15.842  38.359  71.790 -0.00  0.11
ATOM     27  C30 TTB     3      15.774  38.788  70.470 -0.00  0.13
ATOM     28  C32 TTB     3      16.915  39.253  69.830 -0.00  0.14
ATOM     29  C34 TTB     3      18.128  39.288  70.510 -0.00  0.22
ATOM     30  F36 TTB     3      19.230  39.736  69.889 -0.00  0.17
ATOM     31  C33 TTB     3      18.198  38.860  71.829 -0.00  0.32
ATOM     32  C31 TTB     3      17.055  38.395  72.471 -0.00  0.25
ATOM     33  C27 TTB     3      13.900  38.716  73.277 -0.00  0.16
ATOM     34  C24 TTB     3      12.756  38.242  73.910 -0.00  0.19
ATOM     35  C19 TTB     3      10.246  35.227  76.485 -0.00  0.52
ATOM     36  O22 TTB     3       9.666  36.259  76.846 -0.00  0.11
ATOM     37  O21 TTB     3       9.881  33.994  77.008 -0.00  0.17
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ATOM     38  C25 TTB     3       8.461  33.878  77.034 -0.00  0.54
ATOM     39  O16 TTB     3      14.339  33.484  79.037 -0.00  0.10
ATOM     40  H14 TTB     3      12.604  36.740  76.451  0.00  0.07
ATOM     41  H16 TTB     3      13.868  33.718  79.880 -0.00  0.28
END
REMARK   4
REMARK TTP-B Computed low-energy docking mode-4
REMARK Computed Free energy of binding = -10.23kcal/mol
ATOM      1  C1  TTB     4      17.143  39.598  75.386 -0.00  0.31
ATOM      2  C3  TTB     4      17.445  38.517  76.209 -0.00  0.44
ATOM      3  C4  TTB     4      16.386  39.404  74.239 -0.00  0.23
ATOM      4  C7  TTB     4      16.986  37.239  75.892 -0.00  0.48
ATOM      5  C8  TTB     4      15.929  38.132  73.917 -0.00  0.28
ATOM      6  C12 TTB     4      16.224  37.051  74.737 -0.00  0.41
ATOM      7  C2  TTB     4      17.609  40.947  75.720 -0.00  0.27
ATOM      8  C5  TTB     4      16.917  41.727  76.641 -0.00  0.29
ATOM      9  C9  TTB     4      17.367  43.009  76.940 -0.00  0.16
ATOM     10  C13 TTB     4      18.503  43.512  76.315 -0.00  0.18
ATOM     11  C   TTB     4      18.985  44.897  76.631 -0.00  0.12
ATOM     12  F2  TTB     4      17.946  45.676  77.099 -0.00  0.09
ATOM     13  F3  TTB     4      19.942  44.796  77.619 -0.00  0.15
ATOM     14  F4  TTB     4      19.593  45.448  75.524 -0.00  0.03
ATOM     15  C10 TTB     4      19.194  42.733  75.396 -0.00  0.16
ATOM     16  C6  TTB     4      18.747  41.453  75.098 -0.00  0.22
ATOM     17  C11 TTB     4      17.321  36.115  76.808 -0.00  0.49
ATOM     18  O15 TTB     4      18.340  35.448  76.594  0.00  0.20
ATOM     19  N14 TTB     4      16.501  35.815  77.909 -0.00  0.35
ATOM     20  C17 TTB     4      16.864  34.795  78.823 -0.00  0.70
ATOM     21  C18 TTB     4      15.710  33.755  78.814 -0.00  0.52
ATOM     22  C20 TTB     4      14.449  34.240  78.105 -0.00  0.72
ATOM     23  C23 TTB     4      13.472  34.897  78.844 -0.00  0.25
ATOM     24  C26 TTB     4      12.320  35.366  78.223 -0.00  0.39
ATOM     25  C28 TTB     4      12.138  35.180  76.857 -0.00  0.61
ATOM     26  C29 TTB     4      10.923  35.673  76.211 -0.00  0.53
ATOM     27  C30 TTB     4       9.795  34.865  76.154 -0.00  0.51
ATOM     28  C32 TTB     4       8.638  35.328  75.541 -0.00  0.39
ATOM     29  C34 TTB     4       8.609  36.601  74.983 -0.00  0.25
ATOM     30  F36 TTB     4       7.491  37.046  74.388 -0.00  0.10
ATOM     31  C33 TTB     4       9.736  37.411  75.039 -0.00  0.29
ATOM     32  C31 TTB     4      10.895  36.948  75.654 -0.00  0.35
ATOM     33  C27 TTB     4      13.112  34.528  76.111 -0.00  0.36
ATOM     34  C24 TTB     4      14.265  34.061  76.735 -0.00  0.58
ATOM     35  C19 TTB     4      17.003  35.456  80.161 -0.00  0.75
ATOM     36  O22 TTB     4      16.055  36.094  80.636 -0.00  0.01
ATOM     37  O21 TTB     4      18.203  35.360  80.851 -0.00  0.28
ATOM     38  C25 TTB     4      18.897  36.603  80.797 -0.00  0.80
ATOM     39  O16 TTB     4      15.741  35.788  74.375 -0.00  0.06
ATOM     40  H14 TTB     4      15.628  36.342  78.054 -0.00  0.17
ATOM     41  H16 TTB     4      14.949  35.568  74.931  0.00  0.10
END
REMARK   4
REMARK TTP-B Computed low-energy docking mode-5
REMARK Computed Free energy of binding = -8.81kcal/mol
ATOM      1  C1  TTB     5       4.526  31.683  76.605 -0.00  0.33
ATOM      2  C3  TTB     5       5.097  32.667  75.804 -0.00  0.30
ATOM      3  C4  TTB     5       5.268  31.104  77.625 -0.00  0.41
ATOM      4  C7  TTB     5       6.410  33.080  76.022 -0.00  0.31
ATOM      5  C8  TTB     5       6.579  31.509  77.844 -0.00  0.56
ATOM      6  C12 TTB     5       7.152  32.494  77.050 -0.00  0.48
ATOM      7  C2  TTB     5       3.140  31.254  76.392 -0.00  0.29
ATOM      8  C5  TTB     5       2.845  29.923  76.117 -0.00  0.35
ATOM      9  C9  TTB     5       1.526  29.534  75.908 -0.00  0.32
ATOM     10  C13 TTB     5       0.504  30.475  75.970 -0.00  0.26
ATOM     11  C   TTB     5      -0.918  30.059  75.738 -0.00  0.19
ATOM     12  F2  TTB     5      -1.743  30.598  76.705 -0.00  0.04
ATOM     13  F3  TTB     5      -1.306  30.543  74.507 -0.00  0.17
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ATOM	14	F4	TTB	5	-1.004	28.684	75.686	-0.00	0.23
ATOM	15	C10	TTB	5	0.798	31.805	76.246	-0.00	0.14
ATOM	16	C6	TTB	5	2.115	32.193	76.456	-0.00	0.17
ATOM	17	C11	TTB	5	6.976	34.145	75.150	-0.00	0.29
ATOM	18	O15	TTB	5	7.833	33.843	74.311	-0.00	0.18
ATOM	19	N14	TTB	5	6.540	35.476	75.264	-0.00	0.11
ATOM	20	C17	TTB	5	7.023	36.473	74.380	-0.00	0.14
ATOM	21	C18	TTB	5	7.909	37.429	75.225	-0.00	0.23
ATOM	22	C20	TTB	5	9.314	36.895	75.489	-0.00	0.35
ATOM	23	C23	TTB	5	10.230	36.867	74.443	-0.00	0.24
ATOM	24	C26	TTB	5	11.523	36.403	74.656	-0.00	0.30
ATOM	25	C28	TTB	5	11.908	35.965	75.918	-0.00	0.45
ATOM	26	C29	TTB	5	13.268	35.476	76.134	-0.00	0.47
ATOM	27	C30	TTB	5	13.473	34.177	76.583	-0.00	0.49
ATOM	28	C32	TTB	5	14.762	33.707	76.790	-0.00	0.61
ATOM	29	C34	TTB	5	15.852	34.538	76.551	-0.00	0.57
ATOM	30	F36	TTB	5	17.098	34.083	76.755	-0.00	0.57
ATOM	31	C33	TTB	5	15.650	35.837	76.103	-0.00	0.46
ATOM	32	C31	TTB	5	14.357	36.308	75.893	-0.00	0.40
ATOM	33	C27	TTB	5	11.000	35.995	76.969	-0.00	0.41
ATOM	34	C24	TTB	5	9.707	36.461	76.754	-0.00	0.36
ATOM	35	C19	TTB	5	5.817	37.174	73.834	-0.00	0.06
ATOM	36	O22	TTB	5	5.068	37.798	74.596	0.00	0.21
ATOM	37	O21	TTB	5	5.540	37.104	72.475	0.00	0.22
ATOM	38	C25	TTB	5	4.369	37.860	72.178	-0.00	0.01
ATOM	39	O16	TTB	5	8.474	32.873	77.308	-0.00	0.21
ATOM	40	H14	TTB	5	5.863	35.730	75.997	0.00	0.11
ATOM	41	H16	TTB	5	8.626	32.887	78.289	-0.00	0.09
END									

Table 5

Atomic Interactions Between I7L and TTP-A

TTP-A Atom[1]	I7L Atom[2]	Distance (Angstoms)	Interaction type
O2	Cys328 - SG	3.18	Charge
O3	Gly329 - N	3.62	Charge
C10	Trp168 - CB	3.34	Hydrophobic
O8	Asn171 - N	2.86	Hydrogen bond
C12	Met195 - SG	3.74	Hydrophobic
O25	Asn199 – OD1	3.26	Hydrogen bond
H17	Phe236 – O	1.86	Hydrogen bond
C24	Ile203 – CD1	4.79	Hydrophobic
C14	Met195 – SG	3.33	Hydrophobic
O2	Ser240 - OG	3.76	Hydrogen bond

1- Designations for atoms on TTP-A are as shown in FIG. 6
2- Designations for atoms in I7L are as shown in Table 2

Table 6

Atomic Interactions Between I7L and TTP-B

TTP-B Atom[1]	I7L Atom[2]	Distance (Angstoms)	Interaction type
O21	Cys328 - SG	3.07	Electrostatic
C25	Met169 - CB	3.70	Hydrophobic
O22	His241 - N	3.08	Hydrogen bond
O15	Asn171 - N	2.87	Hydrogen bond
H14	Leu239 - O	2.20	Hydrogen bond
O16	Asn171 – ND2	3.50	Hydrogen bond
C26	Leu239 - CA	3.06	Hydrophobic
C27	Met195 - SD	3.24	Hydrophobic
C9	Trp168 – CE3	3.12	Hydrophobic
C5	Leu239 – CD1	3.97	Hydrophobic

1- Designations for atoms on TTP-B are as shown in FIG. 6
2- Designations for atoms in I7L are as shown in Table 2